Published in German on:	AWMF online Das Portal der wissenschaftlichen Medizin

AWMF-Registry No.	001-015	Category:	S3

International guideline on positioning and mobilisation of critically ill patients in intensive care units

S3-Guideline

Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V. (DGAI)

in cooperation with the professional societies

Deutsche Gesellschaft für Chirurgie (DGCH)

Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e.V. (DGF)

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin e.V. (DGIIN)

Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin e.V. (DGNI)

Deutsche Gesellschaft für Physikalische und Rehabilitative Medizin e.V. (DGPRM)

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP)

Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e.V. (DIVI)

Deutscher Verband für Physiotherapie e.V. (ZVK)

Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin (ÖGARI)

Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin (ÖGIAIN)

Version: 1.0

Guideline coordination

Prof. Dr. Stefan J. Schaller, Charité - Universitätsmedizin Berlin, Department of Anaesthesiology an Intensive Care Medicine (CCM/CVK), Berlin, Germany, stefan.schaller@charite.de

Prof. Dr. Dr. Sina M. Coldewey, Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany, sina.coldewey@med.uni-jena.de

Coordinating scientific society

Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V. (DGAI)

Roritzerstraße 27

90419 Nürnberg

Telephone no.: +49 911 933 7828

Coordinating scientific society (mandate holder)

Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI): Thomas Bein; Manfred Blobner; Sina M. Coldewey (entitled to vote for professional society); Julius Grunow; Heidrun Lewald; Stefan J. Schaller; Flora T. Scheffenbichler; Steffen Weber-Carstens; Herrmann Wrigge

Participating scientific or professional societies/organisations (mandate holders)

Deutsche Gesellschaft für Chirurgie (DGCH): Uwe Hamsen

Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e.V. (DGF): Dominik Zergiebel

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN): Carsten Hermes

Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin e.V. (DGNI): Peter Nydahl

Deutsche Gesellschaft für Physikalische und Rehabilitative Medizin e.V. (DGPRM): Anett Reißhauer

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP): Karsten Simon

Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e.V. (DIVI): Arnold Kaltwasser

Deutscher Verband für Physiotherapie e.V. (ZVK): Leonie Renzewitz

Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin (ÖGARI): Roman Ullrich

Österreichischen Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin (ÖGIAIN): Thomas Staudinger

Patient representative

Global Sepsis Alliance: Dennis Kredler

Methodological support

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF):

Methodological advice, moderation of the consensus conference, and implementation of the overall project: Monika Nothacker

Project staff

Charité – Universitätsmedizin Berlin: Alyona Buyukli; Nils Daum; Josephin Meyer; Clara Schellenberg; Linus O. Warner; Aline Grimm; Annika Bald; Felix Baum; Michael Verfuß; Vanessa Arsene; Wiebke Hollstein; Niklas M. Carbon; Maximillian Lindholz; Nicolas Berg

Jena University Hospital: Markus Engelmann; Juliane Götze; Charles Neu; Silke Pfohl

1 What is new?

- Update from S2e to S3
- Evidence assessment Oxford 2011 instead of 2009
- Update of evidence since 2015 with specified PICO questions
- More differentiated consideration of early mobilisation (onset ≤72 h after ICU admission) in the context of ICU mobilisation
- New chapters on assistive devices and neuromuscular electrical stimulation

2 The most important recommendations

- 1.1: We recommend upper body elevation ≥ 40° in intubated patients, considering possible haemodynamic side effects and an increased risk of pressure ulcers. (strong recommendation, LoE 1)
- 1.7: We suggest not using continuous lateral rotation therapy. (weak recommendation, LoE 2)
- 2.1: We recommend prone positioning in invasively ventilated patients with ARDS and limitation of arterial oxygenation (PaO2/FiO2 < 150 mmHg). (strong recommendation, LoE 1)
- 2.3: We recommend performing prone positioning for at least 12 and optimally 16 hours. (strong recommendation, LoE 1)
- 2.13: We recommend awake proning in non-invasively ventilated patients with COVID-19 and acute hypoxic respiratory failure. (strong recommendation, LoE 1)
- 3.1: We recommend early mobilisation of ICU patients within 72 hours of ICU admission. (strong recommendation, LoE 1)
- 3.7: We recommend mobilising patients on extracorporeal membrane oxygenation (ECMO) therapy. (strong recommendation, LoE 3)
- 3.8: We recommend an explicit prescription of medically required immobilisation. (Expert recommendation, LoE 5)
- 5.1: We suggest considering neuromuscular electrical stimulation (NMES) for early mobilisation of critically ill patients. (weak recommendation, LoE 2)

TABLE OF CONTENTS

3 Scope and purpose

3.1 Objective and research question

Mobilisation of critically ill patients in the ICU is an essential part of treatment pathways in today's intensive care medicine. Since the last publication of the S2e guideline in 2015: "Positioning therapy and early mobilization for prophylaxis or therapy of pulmonary dysfunction", new treatment principles have been established. In addition, there is new evidence in many areas of positioning and early mobilization therapy since the last update. This has resulted in the need to revise the currently applicable recommendations while meeting the relevance criteria for guidelines [1].

The aim was to revise the S2e guideline as mentioned above and to adapt it to the current state of research. The new S3 guideline, "International guideline on positioning and mobilisation of critically ill patients in intensive care units" provides high-quality recommendations for positioning and mobilisation therapy, which are safe and have a prognostically positive effect on patient-centred outcomes such as mortality, functionality, quality of life, cognition, duration of ventilation or the length of stay in the intensive care unit and hospital.

3.2 Care structures

The guideline addresses intensive care units as inpatient care structures.

3.3 Patient target group

The guideline refers to critically ill adult patients (≥ 18 years) treated in an ICU.

3.4 Target audience

The guideline is intended for all members of the interdisciplinary and interprofessional treatment team involved in implementing positioning and early mobilisation therapy of ICU patients. This includes physicians from various disciplines, physiotherapists, nurses, occupational therapists and other professional groups. The expert panel's primary concern is

to emphasise the importance of teamwork in positioning and mobilisation therapy. For example, implementing mobilisation is not only the task of a physiotherapist but of all involved in the care. The recommendations of this guideline are based on the state of research published until June 2022.

3.5 Documents related to this guideline

Further documents of the guideline are

- Evidence tables according to Oxford 2011
- Guideline report

These documents can be accessed at: https://register.awmf.org/de/leitlinien/detail/001-015

4 Positioning

This chapter covers upper body elevation, lateral positioning, and continuous lateral rotation therapy (CLRT).

4.1 Upper body elevation

4.1.1 Definition of upper body elevation

There is no clear definition, as its implementation in different studies follows varying criteria. However, upper body elevation is generally defined as an elevation of the upper body more than 30° from the body trunk [2] (Figure 1). Different forms of upper body elevation position can be classified between the sitting position (flexion of the hip and knee joints) on the one hand and the anti-Trendelenburg position (tilting of the entire patient in the supine position) on the other hand (Figure 1). A possible position on this spectrum is the semi-recumbent position, where the patient's upper body and head are raised by a defined number of degrees with flexed hip joints.

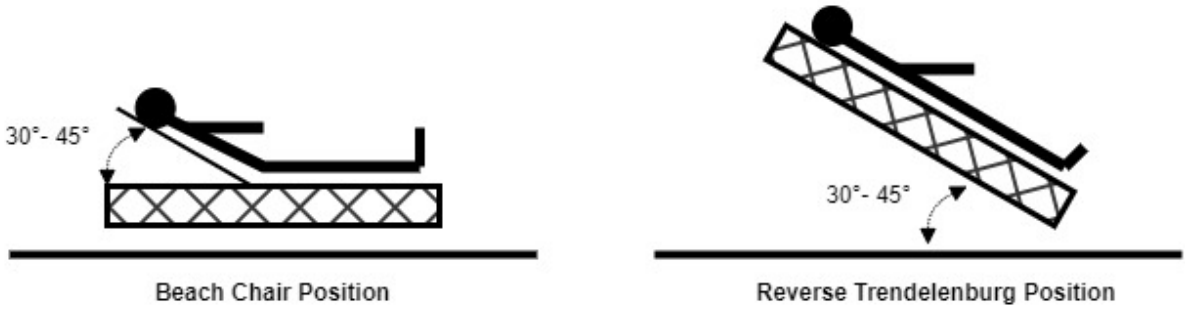

Figure 1. Forms of upper body elevation

Semi-seated position with an elevation angle of 30°-45° (left) and anti-Trendelenburg position with an elevation angle of 30°-45° (right).

4.1.2 Rationale of upper body elevation

Divergent effects of upper body elevation of different organ systems include:

- pulmonary: improved ventilation of the lungs with consecutively improved oxygenation and reduced work of breathing, lower risk of aspiration [3]

- haemodynamic: reduction of venous return, cardiac output, blood pressure, and peripheral oxygenation [4]
- cerebral: reduced intracerebral pressure and perfusion pressure [5]
- abdominal: increased abdominal pressure [6]
- gastrointestinal: reduced reflux and regurgitation [3]
- dermal: increased pressure and risk of pressure ulceration on the rump and heels [3]

4.1.3 Clinical question: Should ICU patients receive upper body elevation?

Recommendation 1.1 (modified 2022)
We recommend elevation of the upper body ≥ 40° in intubated patients, considering possible haemodynamic side effects and an increased risk of pressure ulcers.
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 94%; professional societies 100%
Literature: LoE 1: Wang *et al.* [7]; Pozuelo-Carrascosa *et al.* [8]; Zhuo *et al.* [3] LoE 2: Alexiou *et al.* [9]; Drakulovic *et al.* [10]

Summary of the evidence

Ventilated patients are at increased risk of ventilator-associated pneumonia (VAP), prolonged ICU and hospital length of stay, and increased mortality [3, 7, 8, 11, 12]. Based on physiological considerations, upper body elevation in patients undergoing mechanical ventilation may result in a reduction of pulmonary complications. Possible mediators of this effect include improved gas exchange, better vigilance, and reduced aspiration rate compared with a supine position.

In a Cochrane review of ten moderate-quality randomized controlled trials (RCTs) with a total of 878 ventilated ICU patients, upper body elevation 30-60° versus 0-10° showed significant benefits with respect to clinically suspected VAP (8 studies, 759 patients, 14.3% versus 40.2%, RR 0.36; 95% CI 0.25 to 0.50; risk difference (RD) 25.7%; 95% CI 20.1% to 30.1%). However, no significant benefits were demonstrated for upper body positioning 30-60° versus 0-10° in

terms of microbiologically confirmed VAP, ICU mortality, ICU length of stay, hospital length of stay, ventilator days, antibiotic use, or number of pressure ulcers. There were no significant differences in these parameters when comparing 45° versus 25-30° positioning. Adverse events were inadequately reported [7]. In a meta-analysis including seven high-quality RCTs and 740 ventilated ICU patients the incidences of VAP and gastric reflux were found to be significantly lower in patients with 45° upper body elevation compared with 30° upper body elevation (OR 0.48; 95%CI 0.28 to 0.84; p = 0.009; OR 0.50; 95%CI 0.27 to 0.96; p = 0.04, respectively). However, upper body elevation of 45° compared with 30° also resulted in an increased risk of developing decubital ulcers (OR 1.88; 95%CI 1.05 to 3.36, p = 0.03) [3]. A recent meta-analysis from 2022 analysed eleven studies with 921 ventilated ICU patients comparing upper body elevation with supine positioning. Analyses revealed a reduced VAP incidence (RR 0.38; 95%CI 0.25 to 0.52) and a shorter duration of ventilation (MD -3.26; 95%CI -6.31 to -0.20) compared to the supine position, but no significant benefits for ICU length of stay, hospital length of stay or mortality [8]. A more recent study supports these findings approach [13].

All cited meta-analyses included RCTs with ventilated ICU patients, therefore, generalisability to non-ventilated spontaneously breathing patients may be limited. Upper body elevation measures may be less effective in spontaneously breathing patients, as they are usually more awake and position themselves more easily and generally present with a lower risk of aspiration.

Interpretation of evidence

There is evidence that upper body elevation in intubated patients reduces the incidence of VAP, but not mortality [3, 8]. Therefore, a strong recommendation with a high level of evidence was formulated for patients undergoing invasive mechanical ventilation. In contrast, awake patients do not remain in any position for long periods of time to improve their comfort. This can change the effects of upper body elevation [3], so that the advantages and disadvantages (pressure sores and risk of contracture, pathological/physiological factors, examinations, visits or other activities) should be considered and the positioning should be performed in consultation with the patient.

4.1.4 Clinical question: Should patients with increased intracranial pressure receive upper body elevation?

The assumption that upper body elevation lowers ICP is not always correct. The hydrostatic response to gravity is a complex process and may be disturbed in brain injury. Furthermore, cerebral perfusion pressure (CPP) is dependent on haemodynamics (CPP = MAP - ICP). The expert consensus (S1) Guideline Intracranial Pressure from 2018 (AWMF Register Number: 030/105; valid until Sept. 16, 2022) emphasised that upper body elevation should be performed in an individualised manner and states the importance of regular monitoring of ICP and CPP at 0° (not in case of aspiration risk or ventilation), 15°, and 30° to capture gravity-dependent effects and responses. In all positions, the head should be positioned in a straight position to ensure venous return [5].

Recommendation 1.2 (modified 2022)
We suggest performing upper body elevation in patients with increased ICP to achieve the most favourable effect on cerebral perfusion pressure.
Grade of recommendation: weak
Evidence level: 4 & guideline adaptation/expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline adaptation: intracranial pressure, S1 guideline [5] LoE 3: Burnol *et al.* [14]

4.1.5 Clinical question: Should patients with increased intra-abdominal pressure receive upper body elevation?

Elevated intra-abdominal pressure (IAP) is associated with poorer outcome [6] in ICU patients. Upper body elevation can increase IAP; other influencing factors are increased body mass index (BMI) and body temperature [15, 16]. The effects of increased positive end-expiratory pressure (PEEP) or prone positioning on IAP are incongruent and require further research [17]. In an observational study of 37 ICU patients with 300 measurements of IAP, it was shown that

increasing the upper body from 10° to 20° had little effect on IAP, whereas increasing the upper body from 30° to 45° resulted in a significant increase in IAP [16]. In another observational study of 132 patients, the difference in IAP between 0° and 15° of upper body elevation was shown to be a median of 1.5 (IQR 1.3 - 1.7) mmHg and between 0° and 30° of upper body elevation a median of 3.7 (IQR 3.4 - 4.0) mmHg ($p < 0.001$) [18]. Similar results were also obtained by Vasquez et al. analysing 675 measurements of 45 patients at 0°, 15°, 30°, and 45° upper body elevation and 45° anti-Trendelenburg positioning, with significantly increasing pressures with increased upper body elevation as well as with increasing BMI [15]. Samimian et al. reported similar results of 76 ventilated patients at 0°, 15°, and 30° upper body elevation with an average IAP of 8.4 (SD 4.0), 9.6 (SD 4.5), and 11.1 (SD 4.7) mmHg, respectively [19].

Recommendation 1.3 (modified 2022)
We suggest avoiding upper body elevation with flexion of the knees and hips in patients with elevated IAP or at its risk and suggest favouring the anti-Trendelenburg position for upper body elevation.
Grade of recommendation: weak
Level of evidence: 3 & guideline adaptation
Consensus strength: guideline members 90%; professional societies 91%.
Literature: Adaptation from the guideline Intraabdominal hypertension and abdominal compartment syndrome: updated consensus definition and clinical practice guideline of the World Society for Abdominal Compartment Syndrome ("*Intraabdominale Hypertonie und das abdominale Kompartmentsyndrom: aktualisierte Konsensde)finitionen und klinische Praxisleitlinien der Weltgesellschaft für das abdominale Kompartmentsyndrom*") (6) LoE 3: Vasquez *et al.* [15]; McBeth *et al.* [16]; Cheatham *et al.* [18]; Yi *et al.* [20]

4.1.6 Expert opinion on clinical application

Patients undergoing mechanical ventilation should be correctly positioned such that upper body elevation can achieve its optimal effects. Depending on the patient's own movements, the bedding and the type of mattress elevation of the upper body can lead to the patient slipping downwards, bending at the level of the abdomen or thorax, and consequently to undesirable effects such as difficult breathing. The selection of appropriate materials, the

learning of movement concepts, the education of the patients and the interprofessional and interdisciplinary cooperation help to make optimal use of the upper body elevation and its positive effects.

4.2 Lateral positioning

4.2.1 Definition of lateral positioning

Lateral positioning is defined as positioning in which the body lies on the right or left side rotated 90° around the longitudinal axis.

4.2.2 Rationale of lateral positioning

In addition to relieving pressure points (pressure ulcer prevention), pulmonary complications may be prevented by improving pulmonary gas exchange. An advantage is the simplicity of the measure, which can be carried out at any time with little additional effort [21, 22].

While lateral positioning may not fully provide upper body elevation and the associated benefits of reducing VAP, lateral positioning could lead to other benefits such as improved well-being and sleep quality. A head-down position in the lateral position (lateral Trendelenburg positioning) could also possibly minimise gravity-related mechanisms leading of VAP.

4.2.3 Clinical question: Should ICU patients be placed in lateral positioning?

Recommendation 1.4 (modified 2022)
We are unable to make a recommendation for or against lateral positioning for prevention of pulmonary complications without lung injury.
Grade of recommendation: weak
Level of evidence: 3
Consensus strength: guideline members 95%; professional societies 91%.
Literature: LoE 3: Li Bassi et al. [23]

Summary of the evidence

In a multicentre randomised controlled trial, the effect of lateral 5-10° head-down position (lateral Trendelenburg positioning with side changes every 6 hours) versus upper body elevation to prevent VAP was examined in patients who were to be ventilated for at least 48h [23]. After inclusion of 395 patients, the study was terminated early due to a low VAP incidence, lack of benefits in secondary outcomes, and six serious adverse events (oxygen desaturation, haemodynamic instability, endotracheal extubation, intracerebral haemorrhage, brachial plexus injury) in the lateral Trendelenburg position. In detail, patients receiving lateral Trendelenburg positioning had a lower incidence of VAP (1/194 versus 8/201; RR 0.13, 95%CI 0.02 to 1.03, p = 0.04) while six serious adverse events occurred; however, there was no significant difference in 28-day mortality (60/194 versus 53/201; RR 1.17, 95%CI 0.86 to 1.60, p = 0.32) [23].

Interpretation of evidence

The cited RCT assumed that secretions can flow along the tracheal tube into the lungs, causing VAP. The authors hypothesised that microaspirations could be avoided if the oral tube portion was below the level of the larynx. Therefore, patients in the intervention group were positioned in a 5-10° head-down position in addition to the 90° lateral position. This significantly reduced the risk of VAP but was associated with more serious adverse events.

Furthermore, the desired effects of head-down positioning could be achieved by tubes with subglottic suctioning.

Of note, this recommendation refers exclusively to the lateral position for the prevention of VAP. There may be other indications for lateral positioning, e.g., to rest or sleep, for orientation, to relieve pressure, or to talk to people sitting on one side of the bed [24].

4.2.4 Clinical question: Should ICU patients with unilateral lung injury be placed in lateral position?

Recommendation 1.5 (modified 2022)
We suggest performing a lateral position of about 90° with the healthy side down (good lung down) when ventilating patients with unilateral lung damage to improve gas exchange.
Grade of recommendation: weak
Level of evidence: 3
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 3: Hewitt et al. [25]

Summary of the evidence

In a Cochrane Review of 24 studies on the effect of lateral positioning in intensive care patients, lateral positioning was performed at least once for a minimum duration of ten minutes and compared with other forms of positioning [25]. Due to a high heterogeneity in terms of interventions and endpoints, most studies were not comparable. No study investigated mortality as an endpoint. Data from 8 studies could be analysed but were found to be imprecise. Results of two studies with a total of 19 patients with unilateral lung injury showed that upward positioning of the healthy lung worsened oxygenation by a mean of 50 mmHg compared with downward positioning of the healthy lung (MD -49.3; 95%CI -67.3 to -31.2; $p < 0.001$). However, the power and transferability are limited due to the methodological weaknesses of the included studies [25].

Interpretation of evidence

As shown in the cited Cochrane review, only two studies with a very low sample size are investigated the effect of lateral positioning in ICU patients with unilateral lung injury [25]. The evidence is therefore very limited. In addition, it must be considered that patients should not lie on one side for 24 hours, as this would most likely lead to other adverse effects. Nevertheless, the argumentation that the impaired lung should be positioned upward to achieve a better perfusion-ventilation ratio and to optimize the ventilatory setting is plausible.

As in the section on prone positioning, we recommend adjusting and regularly evaluating positioning based on appropriate parameters such oxygenation, ventilation parameters, and patient comfort.

4.3 Supine position

4.3.1 Clinical question: Should ICU patients be positioned in a flat supine position?

Recommendation 1.6 (modified 2022)
We recommend regular modification of positioning to avoid the flat supine position as an inappropriate form of positioning.
Grade of recommendation: strong
Evidence level: 5 (Expert recommendation)
Consensus strength: guideline members 95%; professional societies 90%.
Literature: [-]

Background

The human body is not made to remain in one position for a long time. Immobilisation in the same position increases the risk of pain, pressure ulcers, circulatory disturbances, contractures, thrombosis, muscle wasting, volume shifts, hormonal dysregulation, and neurocognitive dysfunction with longer duration [26]. Especially the flat supine position should be kept to a minimum and should be limited to interventions that require it. Positioning is a complex intervention that demands biopsychosocial aspects of everyone involved, as well as staff resources, patient environment and technology. Regular repositioning can therefore be made for a variety of reasons and in accordance with patients. The use of concepts such as kinesthetics, basal stimulation, micropositioning and various forms of positioning such as anti-Trendelenburg positioning, semi-mobilising positions as well as technical aids (e.g., motion beds and chairs) can best meet patients' individual needs and requirements [24, 27-29].

4.4 Continuous lateral rotation therapy (CLRT)

4.4.1 Definition of CLRT

CLRT is the continuous rotation of the patient along the longitudinal axis in a motor-driven bed system. Based on the system the rotation angle and duration of rotation can be adjusted.

4.4.2 Rationale of CLRT

The goals of CLRT are the prevention of pulmonary complications (atelectasis, pneumonia, pulmonary secretion congestion), the reduction of pulmonary inflammation because of trauma or infection, and the improvement of pulmonary gas exchange in ventilated patients. The outcomes of interest cover oxygenation, incidence of nosocomial pneumonia, and the duration of ventilation and ICU and hospital LOS. Indications for the use of CLRT include both prophylactic and therapeutic aspects.

CLRT can only be used with deeper sedation, which has negative effects on patients and is not recommended without clinical indication [30].

4.4.3 Clinical question: Should intensive care patients receive CLRT?

Recommendation 1.7 (modified 2022)
We suggest not to use continuous lateral rotation therapy.
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 95%; professional societies 90%.
Literature: LoE 2: Staudinger *et al.* [31]; Schieren *et al.* [32]

Summary of the evidence

Staudinger et al. conducted an RCT in 150 ventilated ICU patients comparing CLRT with usual care for the outcome VAP incidence. In unadjusted analyses, the rate of microbiologically confirmed VAP was significantly lower in the intervention group compared with usual care,

however, after adjusting for sex and factors of severity of illness no statistical significant difference was reached. Notably 39% of patients showed intolerance to CLRT during the weaning phase [31]. In a pilot RCT of 15 patients, preventive CLRT versus usual care showed no benefits for pulmonary complications [33]. A meta-analysis of 8 studies with a total of 422 trauma patients showed a reduction in nosocomial pneumonia for prophylactic CLRT versus usual care (OR 0.33, 95%CI 0.17 to 0.65, p = 0.001), but no effect on existing pneumonia or mortality [32]. These findings align with an older meta-analysis [34].

In a case-control study with a total of 44 traumatology patients, CLRT versus usual care showed no significant benefits in terms of Horowitz index, lung injury, development of pulmonary dysfunction, and other complications. Patients receiving CLRT were more likely to be agitated (Richmond Agitation-Sedation Scale ≥2; 41% versus 9%, p = 0.01) [35]. A retrospective registry analysis of 1476 ventilated patients with lung injury showed no significant improvement of mortality, sepsis incidence, hospital LOS associated with the use of CLRT (n = 239) versus usual care (n = 1237, but a significant association with prolonged duration of ventilation (median 17 (IQR 10 to 26) vs. 14 (8 to 22); p = 0.001), prolonged ICU stay (median 23 (IQR 14 to 32) versus 19 (13 to 28) days; p = 0.002), and higher incidence of organ dysfunction (76.6% versus 67.6%, p = 0.006) [36].

Interpretation of evidence

In the previous version of this guideline published in 2015, CLRT was recommended as an preventive tool for certain patient groups. CLRT requires deep sedation, which affects vigilance and haemodynamics [37-39], and has shown to negatively impact agitation, duration of ventilation, and ICU LOS. Acknowledging the newly available evidence, CLRT can no longer be recommended.

4.5 Prone positioning

4.5.1 Definition of prone positioning

Proning is defined as positioning in which the body is turned prone by 180° around the longitudinal axis. A different positioning form is incomplete proning, in which the patient is rotated ≥ 135° and < 180° from the supine position.

4.5.2 Rationale of prone positioning

Prone positioning has multiple physiological effects that may have a positive impact on the respiratory situation of patients with ARDS. In several animal studies with experimentally induced lung injury, prone positioning reduced the incidence of lung injury and oedema with a magnified effect in the dependent lung regions [40, 41]. Galiatsou et al. showed that prone positioning following a recruitment manoeuvre in supine position improved lung ventilation homogeneity by reducing non-aeriated and overinflated lung areas [42]. This effect has also been demonstrated in patients with COVID-19-related ARDS [43]. Katira et al. identified an increase in pleural pressure (leading to a reduced transpulmonary pressure), and a reduction in the pleural pressure gradient, which lead to homogenisation of pulmonary ventilation and reduce the difference in regional compliance of dependent and non-dependent lung segments [44]. This had a beneficial effect on lung recruitment and reduction of tidal recruitment during ventilation cycles and reduced end-inspiratory hyperinflation, particularly in non-dependent lung segments [45]. A relevant ventilation-perfusion-mismatch is an essential problem in the management of patients with ARDS. Spinelli et al. showed that the ventilation-perfusion mismatch is an independent predictor of mortality in ARDS patients [46]. Prone positioning leads to an improved ventilation-perfusion ratio assessed by electrical impedance tomography in ARDS patients [45]. In a study published by Wang et al. prone positioning improved ventilation-perfusion ratio correlated with increased oxygenation [47].

The initial assumption was, that the main effect of prone positioning resulted from improved oxygenation, however, evidence suggests that there is no relationship between improved oxygenation and survival. In a secondary analysis of the PROSEVA trial, there was no difference in the change of PaO_2/FiO_2 between those patients who survived and those who died. In detail,

in 63% of survivors oxygenation improved and in 37% of them it worsened prone position, and within decedents, 66% showed improved oxygenation and 34% worsened oxygenation [48]. A possible explanation is that the mortality benefit is achieved by reducing ventilator-associated lung injury.

4.5.3 Clinical question: When should prone positioning be performed (indication of prone positioning)?

The PROSEVA trial by Guérin et al. can be considered a milestone study in the field of prone positioning [49]. Based on the relevant findings of previous studies including the severity of ARDS, the compliance with lung-protective ventilation, and the duration of prone positioning, the PROSEVA study was designed. By protocol, this multicentre randomized controlled trial included ARDS patients with a duration of ventilation < 36h and a PaO2/FiO2 < 150 mmHg with a FiO2 ≥ 0.6, a PEEP ≥ 5 cmH2O, and a tidal volume of approximately 6 ml/kg predicted bodyweight (PBW). Patients who were randomised to the intervention group received at least 16h of prone positioning daily. This scheme continued until patients achieved a PaO2/FiO2 > 150 mmHg with a PEEP ≤ 10 cmH2O and a FiO2 ≤ 0.6, or until day 28. A total of 466 patients was studied. Despite randomisation and likely influenced by the prone position, less patients received vasopressors and had a lower Sequential Organ Failure Assessment (SOFA) Score in the intervention group, while more patients received neuromuscular blockade. Patients received an average of four cycles of prone positioning with a mean duration of 17h. The primary endpoint 28-day mortality showed a significant survival advantage for the intervention group of 16.0% versus 32.8% ($p < 0.001$) in the control group. This result remained stable after adjusting for SOFA Score, vasopressor requirement, and neuromuscular blockade. In addition, there was better oxygenation and an increased rate of successful extubation in the intervention group [49]. In a secondary analysis of the PROSEVA study prone positioning did not lead to a reduction in VAP incidence [50].

Comprehensive meta-analyses [51-60] on prone positioning include 12 years of intensive research beginning in 2001 with a study by Gattinoni et al. [61] and ending with the 2013 PROSEVA study by Guérin et al. [49]. The comparison of these two papers reflects the evolution of knowledge regarding prone positioning. The results of the PROSEVA study have

an important influence on the outcome analysis in various meta-analyses. Of note, since no RCTs have been published after the PROSEVA study, the more recent systematic reviews and meta-analyses all work with the same evidence base [49].

Moran et al. recently published a meta-analysis on the effect of prone positioning on mortality in ARDS patients, which found significant heterogeneity for the outcome mortality in three defined time periods (28-30 days: I2 = 69%, p < 0.01; 2-3 months: I2 = 64%, p < 0.01; 6 months: I2 = 30%, p = 0.23), with prone positioning providing no survival benefit at any of the indicated time periods [62]. Studies with a high risk of bias (missing ARDS diagnosis, paediatric patients, inconsistent ventilation modes, no control group) were excluded. Prone positioning ≥ 12 h, limitation of tidal volumes (lung-protective ventilation), and moderate or severe ARDS (PaO2/FiO2 < 200 mmHg) were predictors of decreased mortality. Furthermore, prone positioning was associated with increased survival at cut-off values of ≥12 h duration, ≤8.5 ml/kg tidal volume, and PaO2/FiO2 ≤130 [62].

Multiple additional meta-analyses exist showing among other endpoints an increased risk of pressure ulcers, tube obstruction or airway problems, and dislocation of chest tubes [51-59].

Recommendation 2.1 (modified 2022)
We recommend prone positioning in invasively ventilated patients with ARDS and impaired arterial oxygenation (PaO2/FiO2 < 150 mmHg).
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline references: Cho *et al.* [63]; Hashimoto *et al.* [64]; Fan *et al.* [65] LoE 1: Moran *et al.* [62]; Munshi *et al.* [51]; Fan *et al.* [65]; Beitler *et al.* [53]; Alsaghir *et al.* [66]; Lee *et al.* [57]; Wang *et al.* [58]; Longobardo *et al.* [59] LoE 2: Guérin *et al.* [49, 50]; Mora-Arteaga *et al.* [56]; Abroug *et al.* [67]; Taccone *et al.* [68]; Cao *et al.* [52]; Sud *et al.* [69]; Sud *et al.*[55]; Sud *et al.* [54]; Kopterides *et al.* [60]; Mancebo *et al.* [70]; Tiruvoipati *et al.* [71]

4.5.4 Clinical question: When should prone positioning be initiated?

In a Cochrane review by Bloomfield et al. a subgroup analysis revealed a positive effect on short- and long-term mortality if patients were placed in prone position within 48h of start of invasive mechanical ventilation [72]. These results are congruent with the previously listed meta-analysis by Mora-Arteaga et al. [56]. In the PROSEVA trial, prone positioning was started on average within 37h of the start of invasive ventilation, implying indirect evidence for this time frame [49].

There are currently no studies explicitly investigating the optimal time to start prone positioning. However, all available studies and the positive physiological effects indicate that initiating it immediately after its indication is the optimal approach.

Recommendation 2.2 (modified 2022)
We recommend considering prone positioning at an early stage and implementing it as soon as it is indicated
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: Fan *et al.* [65] LoE 1: Munshi *et al.* [51]; Bloomfield *et al.* [72] LoE 2: Guérin *et al.* [49]; Mora-Arteaga *et al.* [56]; Mancebo *et al.* [70]

4.5.5 Clinical question: How long should the patient be positioned in prone position?

No RCTs comparing different prone positioning protocols exist. Therefore, a recommendation on the duration of a prone positioning cycle can only be made based on the comparison of individual studies and the resulting meta-analyses.

The duration of individual prone positioning in the different studies ranges from 7h to 40h [49, 51, 54, 56, 62, 72, 73].

Most subgroup analyses of meta-analyses (Moran [62], Munshi [51], Beitler [53], Mora-Arteaga [56] and Longobardo [59]) have found a significant survival benefit using a cut-off of

12 hours. In contrast, Sud et al. [54] and Lee et al. [57] defined 16 and 10 hours as the minimum duration, respectively, and found a survival advantage with longer duration of prone positioning. When increasing the minimum duration from 10 to 16 hours, the allocation of only one study changes having no impact on the results (Voggenreiter et al. [74]). Moran et al. additionally performed a meta-regression, showing a positive effect for each additional hour of prone positioning (RR 0.97, 95%CI 0.96 to 0.98, p < 0.001) [62].

According to the available evidence, a minimum duration of 12h is necessary to achieve the beneficial effects of prone positioning, while each additional hour improves them~~,~~ although the effect of a duration longer than 16 hours has not yet been specifically investigated [49].

Recommendation 2.3 (modified 2022)
We recommend prone positioning for at least 12, preferably 16 hours.
Grade of recommendation: strong
Evidence level 1
Consensus strength: guideline members 100%; professional societies 100%
Literature: LoE 1: Moran *et al.* [62]; Munshi *et al.* [51]; Mora-Arteaga *et al.* [56]; Bloomfield *et al.* [72]; LoE 2: Guérin *et al.* [49]; Sud *et al.* [54]

4.5.6 Clinical question: How should ventilator parameters be set during prone positioning?

The goal of ventilation in ARDS is to ensure oxygenation and decarboxylation of the patient while preventing or minimizing further lung injury from ventilation. Prone position itself is an important part of the lung-protective ventilation strategy.

Tidal volume

The limitation of tidal volumes to 4 - 8 ml/kg PBW in patients with ARDS is strongly recommended according to the official guideline of the American Thoracic Society, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine [65, 75, 76]. Subgroup analyses of meta-analyses suggest that limitation of tidal volume is a necessary prerequisite for the mortality benefit from prone positioning (see chapter 4.5.3). While a

majority of the meta-analyses have used a cut-off of 8 ml/kg predicted body weight (PBW), there is evidence suggesting that lowering this cut-off has a beneficial effect [75].

Positive post-expiratory pressure (PEEP)

The physiological effects of prone positioning in ARDS patients lead improved compliance and recruitment, as well as decreased non-ventilated lung areas, hyperinflation, and recruitment-derecruitment during respiratory cycles [45]. Gainnier and colleagues were able to show that prone positioning and PEEP have an additive effect on improved oxygenation [77], leading to the rationale to also set an optimal PEEP during prone position. The setting of optimal PEEP in the supine position is the subject of current research projects; specific evidence on the optimal PEEP setting in the prone position is lacking. Therefore, we refer to the recommendations for supine position of the S3 guideline "Invasive ventilation and use of extracorporeal procedures in acute respiratory failure" (AWMF register number 001-021) [78].

Spontaneous breathing

Although deepened sedation and analgesia are commonly used in the prone position to avoid discomfort, spontaneous breathing is also possible during prone positioning [65].

Recommendation 2.4 (modified 2022)
We recommend applying the generally recommended principles of optimised ventilation for ventilation in the prone position, including the limitation of tidal volumes, prevention of derecruitment, and integration of spontaneous breathing components.
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: S3 guideline „Invasive ventilation and use of extracorporeal procedures in acute respiratory failure.“ (65); Cho *et al.* [63] LoE 1: Moran *et al.* [62]; Wang *et al.* [58]; Bloomfield *et al.* [72]; Munshi *et al.* [54]; LoE 2: Cao *et al.* [52]; Sud *et al.* [54]; Mora-Arteaga *et al.* [56]

4.5.7 Clinical question: How should prone positioning be prepared?

Various studies have shown that prone positioning does not leads to hypotension or cardiac instability. In an observational study by Jozwiak et al. 18 patients with ARDS were examined regarding hemodynamic and respiratory changes in association with prone positioning [79]. In 50% of patients, prone positioning resulted in an increase of cardiac index of more than 15% from a median of 3.0 to 3.6 l/min/m2, whereas there was no significant change in the remaining 9 patients. Patients with an increase in cardiac index due to prone positioning showed sufficient preload reserve in the passive leg raise test before the intervention [79]. These results were confirmed by Ruste et al. analysing 197 measurements of 107 patients transferred to prone position; cardiac index increased in 25%, decreased in 23% and did not change in 52% of prone positions [80]. The entire cohort showed no change during prone positioning, however, a significant decrease in cardiac index was detected during repositioning to supine. In this setting an increased mean arterial pressure was detected in two studies alongside an improved cardiac index [81, 82]. In the PROSEVA trial, there was a significantly lower number of cardiovascular arrests in the intervention group [49]. The physiological basis of the increase in cardiac index is the improved preload and the reduced pulmonary vascular dysfunction [80]. The effect on pulmonary vascular resistance was studied

by Vieillard-Baron et al.; in an observational study with 21 ARDS patients with acute cor pulmonale right ventricular function significant improved during prone positioning [83].

In summary, the studies on the hemodynamic effects of prone positioning in patients with ARDS show that the intervention is hemodynamically well-tolerated and may also have positive effects on right ventricular load. Nevertheless, the volume status of patients should be optimised prior to positioning. Studies on the relevance of vasopressor therapy in the context of prone positioning are lacking. Due to the lack of negative hemodynamic effects of prone positioning, ongoing vasopressor therapy is not a contraindication according to the expert panel.

Recommendation 2.5 (modified 2022)
We suggest stabilising the patient haemodynamically and optimising volume status prior to prone positioning. The use of catecholamines is not a contraindication for prone positioning.
Grade of recommendation: weak
Level of evidence: 5 (Expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: [-]

4.5.8 Clinical question: When should prone positioning critically evaluated?

Prone positioning and intra-abdominal pressure

In addition to pulmonary and cardiovascular systems, prone positioning also affects intra-abdominal organs. It has been shown that prone positioning increases intra-abdominal pressure in patients with ARDS. In a prospective observational study by Hering et al., intraabdominal pressure measured by bladder pressure increased from a mean of 12 ± 4 mmHg to 14 ± 5 mmHg. Alongside an increased intra-abdominal pressure, a reduction of the renal component of the cardiac index and an increase in renal vascular resistance was found. The overall increase in cardiac index did not result in any restriction of renal perfusion, as indicated by the preserved renal function [82]. Furthermore, it was shown that the increase in intra-abdominal pressure had no effect on liver function or splanchnic perfusion [81, 84].

Because of its effects on intra-abdominal pressure, Gaudry et al. studied the effects of prone positioning in patients undergoing abdominal surgery. This retrospective analysis of 36 patients indicated no increased risk for surgical complications associated with prone positioning [85].

Obesity is a global health problem and a common comorbidity in ICU patients. In particular, abdominal obesity may modify the effects and the implementation of prone positioning. Weig et al. studied the impact of abdominal obesity on mortality, liver function, and renal function in the setting of prone positioning. They demonstrated in 82 patients with ARDS (41 with abdominal obesity and 41 without abdominal obesity) that there was a significantly higher rate of hypoxic hepatitis (22% versus 2%; $p = 0.015$) and renal failure (83% versus 35%; $p < 0.001$) in the abdominal obesity group after a cumulative 41 hours of prone positioning, whereas there was no difference in mortality (34% versus 34%; $p > 0.99$). There was no effect on renal failure or hypoxic hepatitis in the interaction analysis between abdominal obesity and prone positioning, but there was an effect on mortality. In the baseline characteristics, patients with abdominal obesity were significantly more likely to have arterial hypertension (32% versus 5%; $p = 0.002$) as a concomitant disease and significantly less likely to have trauma as a cause of ARDS [86]. In addition, obesity is an independent risk factor for renal failure in critically ill patients [87]. According to the findings of DeJong et al., prone positioning is feasible in overweight patients (BMI ≥ 35 kg/m2) and is not associated with higher complication rates. The overweight patients responded better to prone positioning with oxygenation and had significantly lower mortality at day 90 [88].

Prospective studies on the subject of prone positioning in patients with ARDS and obesity are currently lacking. Accordingly, the possible positive effects of prone positioning in obese patients or patients who underwent abdominal surgery should be critically evaluated.

Recommendation 2.6 (modified 2022)
We suggest considering prone positioning in patients following abdominal surgery, patients with abdominal pathologies, or patients with abdominal obesity after individual consideration of benefits (improvement in oxygenation) and risks (increase in intra-abdominal pressure with risk of surgical complication, acute renal failure or hypoxic hepatitis)
Grade of recommendation: weak
Level of evidence: 4
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 3: Hering *et al.* [82] LoE 4: Gaudry *et al.* [85]; Weig *et al.* [86]; DeJong *et al.* [88]

Prone positioning in patients with intracerebral lesions

Prone positioning has important influence on haemodynamics and may thus also affect the dynamics of intracerebral perfusion and pressure. The RCT by Beuret et al. investigated whether prone positioning has a protective effect in comatose patients. In the 24% of patients who received continuous intracranial pressure (ICP) monitoring, there was a significant increase in ICP from 11 mmHg to 23.7 mmHg during prone positioning [89]. These observations were confirmed by Roth et al. in their retrospective case series of 29 patients with a severe intracranial lesion during prone positioning due to respiratory failure. A significantly higher mean ICP was found during prone positioning, as well as significantly more episodes with an ICP > 20 mmHg or a cerebral perfusion pressure (CPP) < 70 mmHg. However, patients benefited from prone positioning in terms of oxygenation [90]. Reinprecht et al. confirmed that in patients with subarachnoid haemorrhage who received prone positioning for ARDS, ICP, as well as frequency of episodes with an ICP > 20 mmHg or a CPP < 60 mmHg increased. Interestingly, despite this, there was an improvement in systemic and brain oxygenation, these findings lead the authors to conclude that the improvement in oxygenation outweighed the negative hemodynamic effects on ICP [91]. Similar results have been presented by Nekludov et al. [92].

Thelandersson et al. found no difference in ICP in prone position. Only one of eleven patients did not tolerate the prone position and had to be re-positioned to supine position due to an increased ICP and a decreased CCP [93].

Based on the available evidence, a recommendation concerning patients with acute cerebral lesions and prone positioning in ARDS is currently not possible [94]. It is required to make an individual decision and weigh the potential harms of an increased ICP or a decreased CCP against the benefits of improved oxygenation and its effect on cerebral oxygenation. If prone positioning is performed, continuous monitoring of the relevant parameters (ICP and CCP) is necessary. Furthermore, to preserve venous outflow, lateral rotation of the head should be avoided.

Recommendation 2.7 (modified 2022)
We recommend that patients at risk of increased ICP are monitored continuously or closely during prone positioning. The head should be positioned in a centred position and lateral rotation should be avoided.
Grade of recommendation: strong
Level of evidence: 5 (Expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Beuret *et al.* [89] LoE 3: Wright *et al.*[94]

Further consideration for prone positioning

While prone positioning is recommended in moderate to severe ARDS, patients may present with other comorbidities, which implies that potential benefits and risks have to be considered on an individual basis. Especially in patients with an open abdomen, an unstable spine, increased intracranial pressure, hemodynamically effective cardiac arrhythmias, or shock, a multiprofessional and interdisciplinary consensus should be found that weighs the potential benefit against the risk when determining the indication.

Recommendation 2.8 (modified 2022)
We suggest that prone positioning should only be carried out in individual cases after considering risks and benefits in an interdisciplinary fashion involved when the following contraindications exist: - open abdomen - spinal instability - increased intracranial pressure - cardiac arrhythmias with haemodynamic consequences - shock
Grade of recommendation: weak
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Beuret *et al.* [89]

4.5.9 Clinical question: When can prone positioning be stopped?

When prone positioning cycle therapy can be stopped has not yet been specifically investigated. Accordingly, protocols of the available studies can be used.

In the PROSEVA study, prone positioning was performed until there was an improvement in oxygenation ($PaO_2/FiO_2 \geq 150$) under de-escalated ventilation (PEEP ≤ 10 cmH_2O and $FiO_2 \leq 0.6$) four hours after supine positioning. Based to the survival benefit found in the PROSEVA trial, this approach is currently recommended [49].

Recommendation 2.9 (modified 2022).
We suggest terminating prone positioning if improvement in supine oxygenation persists (4 hours after repositioning: $PaO_2/FiO_2 \geq 150$ with a PEEP ≤ 10 cm H_2O and a $FiO_2 \leq 0.6$).
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Guérin *et al.* [49]

Due to the lack of evidence as to whether and for how long prone positioning should be performed in non-responders, we suggest as a pragmatic expert recommendation that prone positioning therapy should be terminated after two unsuccessful attempts (= lack of improvement in oxygenation). This does not exclude that in the individual course of the

disease a new attempt of prone positioning therapy is made at a later time or that according to individual indication prone positioning can still be performed even after two attempts.

Recommendation 2.10 (modified 2022)
We suggest that prone positioning therapy should be discontinued if at least two positioning attempts have been unsuccessful.
Grade of recommendation: weak
Evidence level: 5 (Expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: [-]

4.5.10 Clinical question: Is the complete prone position to be favoured over the incomplete prone position?

The incomplete prone position is frequently used, as it reduces supposed side effects by reducing pressure on the abdomen and face. Scientific studies on this type of prone positioning are scarce. In particular, studies on the effect of prone positioning in general have explicitly used complete prone positioning (180°). This also applies to the protocol of the PROSEVA study, which is the only study to show a significant reduction in mortality in the prone positioning group [49]. The only study specifically investigating complete vs. incomplete prone position is the RCT by Bein et al. from 200. It randomized 52 patients in a cross-over design in which one group received incomplete (135°) followed by complete (180°) prone positioning for 6 hours respectively, while the second group received first complete and then incomplete prone positioning for 6 hours each. Study results showed that complete prone positioning had a more pronounced effect on oxygenation. Patients with severe ARDS had an increased oxygenation (improvement of P/F ratio ≥ 20%) in 91.6% when complete prone positioning was performed, and 57.1% during incomplete prone positioning. There was no difference in the incidence of pressure sores, however, the incidence of facial oedema was 10% lower during incomplete prone position (59.2%) compared with complete prone position [95].

Based on the magnified effect on oxygenation of complete vs. incomplete prone position [95] and evidence for a reduction in mortality for prone vs. supine position [49], the complete is preferable to the incomplete prone position.

Recommendation 2.11 (modified 2022)
We recommend complete (180°) rather than incomplete prone positioning as there is no evidence to improve clinical outcomes for incomplete prone positioning and complete prone positioning has a stronger effect on oxygenation.
Grade of recommendation: strong
Level of evidence: 2
Consensus strength: guideline members 95%; professional societies 91%.
Literature: LoE 2: Bein *et al.* [95]

4.5.11 Clinical question: What are the risks and side effects of prone positioning?

Prone positioning causes a redistribution of the weight to parts of the body that not normally exposed in healthy individuals. Systematic reviews with meta-analysis and randomized controlled trials have repeatedly shown that prone positioning significantly increases the risk of pressure ulcers [52, 54, 72, 96-98]. The risk ratio in two systematic reviews with meta-analysis was increased 1.23-1.27-fold, and pressure ulcers were recorded in approximately 30% of cases [52, 54, 98-101]. In accordance with the significantly increased risk, it is recommended to carefully check the endangered sites regularly during prone positioning. Possible localisations of pressure sores and ulcers are shown in Figure 2.

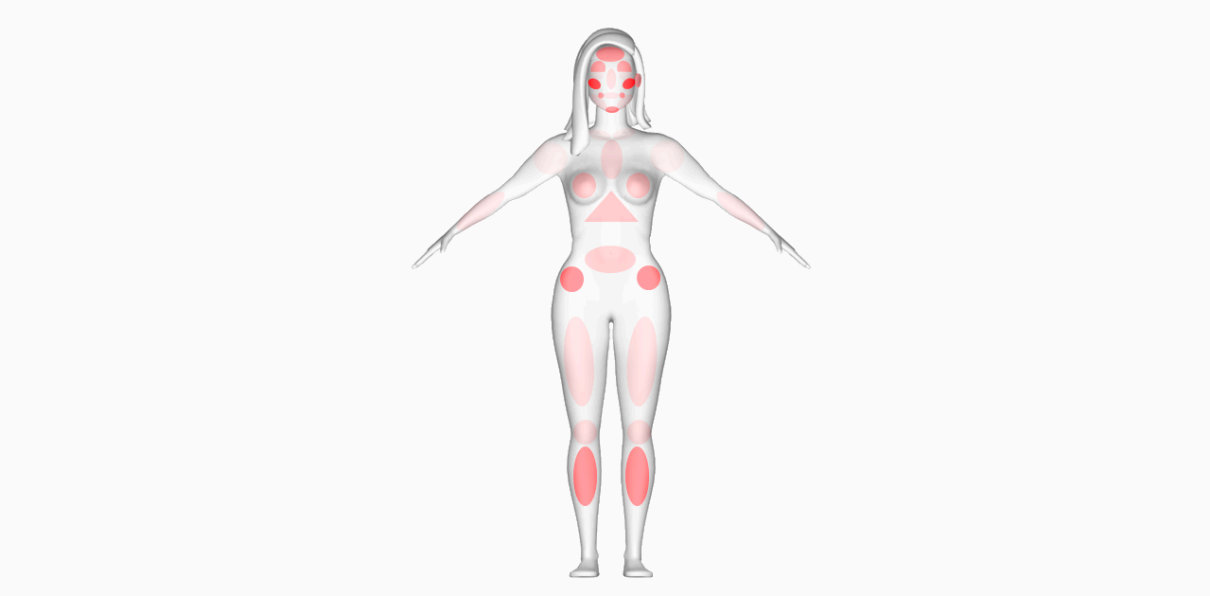

Figure 2. *Frequency and localisation of pressure ulcers by region.*

By Kornappel S, based on Elmer N et al. [100]. Sites of pressure ulcers in order of descending frequency: zygomatic bone, chin, iliac crest, lower leg, corner of mouth, forehead, eyeball/eyelid, ear, thorax, breast, abdomen, nose, sternum, thigh, knee, lower lip, mandible, forearm, cornea, shoulder, clavicle [100].

Recommendation 2.12 (modified 2022)
We recommend to carefully examine the areas at risk for pressure ulcers during prone positioning to minimise the risk of development.
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: Hashimoto *et al.* [64]; Fan *et al.* [65]; LoE 1: Bloomfield *et al.* [72]; LoE 2: Cao *et al.* [52]; Sud *et al.* [54]; Patton *et al.* [97]

4.5.12 Clinical question: Is awake proning useful during non-invasive ventilation?

In their systematic review, Li et al. included a total of 29 studies on prone positioning in awake and non-intubated COVID-19 patients. Of these, ten RCTs were included in a meta-analysis. The included studies show great heterogeneity in terms of treatment site (ICU versus normal ward), respiratory therapy at inclusion (oxygen insufflation, high-flow oxygen therapy, or non-invasive ventilation), and type and duration of awake prone positioning (one hour to

maximum tolerated duration). It remains unclear whether complete or incomplete prone positioning was performed in the respective studies. In the randomized controlled trials, there was a significant reduction in the need for intubation (RR 0.84, 95% CI 0.72 to 0.97) when awake prone positioning was used. Subgroup analyses demonstrated this effect in patients treated in an ICU-setting or when high-flow oxygen therapy or non-invasive ventilation were used. In contrast, no effect was found in patients treated on the ward or with conventional oxygen therapy. No effect was found in the meta-analysis in the randomized controlled trials regarding mortality, length of stay in the intensive care unit and hospital stay [102].

Schmid et al. conducted a systematic review with meta-analysis of awake prone positioning in patients with COVID-19 in an ICU. Two studies with a total of 1196 patients were included. A beneficial effect was found for the endpoint intubation or 28-day mortality. However, when looking at the endpoints independently, awake proning reduced intubation rate within 28 days whereas no effect of 28-day mortality was observed [103].

In contrast, Beran et al. included RCT and observational studies in their systematic review with meta-analysis. There was a significant effect of awake proning on mortality rate (RR 0.68, 95% CI 0.51 to 0.90), but no effect on hospital length of stay was found [104]. Similarly no effect of awake proning on intubation rates could be demonstrated, but this effect was visible in a subgroup analysis including only RCTs (RR 0.83 [95% CI 0.72-0.97]; p = 0.02, I2 = 0%). The effect of awake proning on mortality was also confirmed in a meta-analysis by Fazzini et al. [105].

The meta-trial consisting of six RCTs by Ehrmann et al. included 1126 patients with hypoxic respiratory failure due to COVID-19 and high-flow oxygen therapy. Patients were randomised to the prone position or usual care. In the intervention group patients were encouraged to spend as much time as possible in the prone position which led to an average of 5 hours per day. The primary endpoint of "death or intubation within 28 days" was significantly lower in the prone positioning group (40%) compared with 46% in the control group (RR 0.86, 95% CI 0.75 to 0.98). No effect on hospital length of stay or 28-day mortality was shown. The effect on intubation rate remained present when analysed individually [106].

The randomised controlled trial by Alhazzani et al. included patients with COVID-19 and requirement for low-flow oxygen with an FiO2 ≥0.4 or non-invasive ventilation. Randomisation was stratified based on impairment of oxygenation. Patients in the intervention group were instructed to lie prone for 8-10 h daily with 2-3 breaks. A total of 400 patients were randomised. There was no difference in the intubation rate within 30 days. In the subgroup analysis of patients with high-flow oxygen therapy at inclusion, a significant reduction in intubation rate was found [107]. The RCTs by Rosén et al. and Fralick et al. showed no advantage for prone positioning of patients with COVID-19 while awake [108, 109].

Overall, prone positioning was shown to have few side effects in awake patients [106, 107].

The various meta-analyses describe a beneficial effect of prone positioning while awake with regard to the lower intubation rates in COVID-19 patients. Accordingly, it is recommended to perform this measure in this patient population. A recommendation with regard to other causes of hypoxic lung failure is currently not possible due to lack of evidence.

Recommendation 2.13 (new 2022)
We recommend awake proning in non-invasively ventilated patients with COVID-19 and acute hypoxic respiratory failure.
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: "S3 Guideline – Recommendations for inpatient treatment of patients with COVID-19" (AWMF Registry Number 113-001LG) [110]. Effect: LoE 2: Li *et al.* [102]; Schmid *et al.* [103]; Beran *et al.* [104]; Ehrmann *et al.* [106]; Fazzini *et al.* [105]; Ibarra-Estrada *et al.* [111] No effect: LoE 2: Alhazzani *et al.* [108]; Fralick *et al.* [108]; Rosen *et al.* [109]

Recommendation 2.14 (new 2022)
We are unable to make a recommendation for or against awake proning in non-invasively ventilated patients without COVID-19.
Grade of recommendation: [-]
Level of evidence: 5 (expert consensus)
Consensus strength: guideline members 88%; professional societies 100%.
Literature: [-]

4.5.13 Clinical question: How long should awake prone positioning be performed?

Within the different studies performed on prone positioning in non-intubated COVID-19 patients, very heterogeneous protocols were applied. In their systematic review, Li et al. reported a duration between one hour and the maximum tolerated time [102].

In their systematic review with meta-analysis, Ponnapa et al. were able to show that awake prone positioning improved oxygenation, but they are unable to find a dose-response relationship in relation to longer duration or more frequent prone positioning [112].

Tan et al. were able to confirm the improved oxygenation in their systematic review but found no effect of duration of awake prone positioning on oxygenation. Only the respiratory rate was significantly lower in patients who received prone positioning for more than five days [113].

In the meta-trial of six RCTs by Ehrmann et al., patients with awake prone positioning had lower intubation rates. Patients were in prone position for an average of 5 hours per day [106]. The study by Esperatti et al. showed an advantage in terms of mortality at > 6 hours duration, with a magnified effect above 8 hours [114]. The systematic review by Fazzini et al. showed a mortality benefit at an average duration of 4 hours [105].

Due to the heterogeneity of results, no recommendation can be made at this point regarding the duration and frequency of prone positioning while awake.

Recommendation 2.15 (unchanged 2022)
We are unable to make a recommendation for the duration of awake proning.
Grade of recommendation: [-]
Evidence level: 5 (expert consensus)
Consensus strength: guideline members 95%; professional societies 91%.
Literature: LoE 2: Li *et al.* [102]; Ponnapa *et al.* [112]; Tan *et al.* [113]; Fazzini *et al.* [105]

4.5.14 Clinical question: Should prone positioning be performed during ECMO therapy?

In severe ARDS with refractory hypoxaemia, ECMO and prone positioning may both be indicated. The question of whether prone positioning is useful during ECMO therapy was investigated by Papazian et al. in a systematic review. Specifically, they addressed whether patients on veno-venous ECMO (vv-ECMO) with prone positioning had improved outcome.

Thirteen studies were included, of which one study had a randomized controlled design, and the 12 remaining studies were observational. Prone positioning additive to vv-ECMO showed a significant survival benefit at different time points, e.g., after 28 days and at hospital discharge [115]. Poon et al. performed a similar systematic review and found no survival benefit in an adjusted analysis. In contrast, patients with vv-ECMO and prone positioning had a longer ECMO duration and a longer ICU stay. No severe complications were reported [116]. Pooled individual patient data analysis from several observational studies showed no benefit in an adjusted analysis, while a propensity score matched cohort showed a survival benefit within 60 days [117].

Based on the available literature including current evidence in COVID-19 patient and the safe applicability, we recommend prone positioning of ARDS patients with vv-ECMO in centres with experience, risk management and appropriate equipment [115, 118-122].

Recommendation 2.16 (new 2022)
We suggest performing prone positioning in ARDS patients with veno-venous ECMO therapy.
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Effect: LoE 2: Papazian *et al.* [115] No effect: LoE 2: Giani *et al.* [117]

4.5.15 Clinical question: How should prone positioning be performed practically?

Although implementation of prone positioning is a complex and challenging task, especially considering the connection to various medical devices (e.g., ventilators, dialysis, ECMO, perfusion pumps), there is no scientific evidence on how prone positioning should be technically performed.

After the indication has been established, all team members should be informed. The size of the team depends on the weight of the patient as well as the complexity of the positioning due to the medical equipment and accesses already mentioned. Each team member should have a specific task, such as securing the ventilator access or turning the critically ill patient at the hip. Then the patient should be prepared for positioning. For this purpose, all accesses

(e.g., ventilatory access, vascular accesses, drains) should be checked and secured. In addition, the critically ill patient should be preoxygenated to avoid desaturation during the positioning measure. If used, storage materials should be prepared.

Before positioning, a team-time-out can be performed to ensure that all preparations have been completed and all team members know their tasks.

There are several ways to perform the positioning. The patient can first be moved laterally, turned to a 90° angle and in a last step rotated to 180°. Aids such as sliding film and anti-slip film can be used. Another option is to wrap the patient with a second bed sheet from ventrally and then turn en bloc with help of the bed sheet. Of note, this rapid change in position can lead to more circulatory effects. Videos of prone positioning can be found in the appendix of two papers by Guérin et al. [49, 123], which used no additional positioning materials.

Studies on the advantages and disadvantages of using positioning materials are very limited. A study by Chiumello et al. shows that the use of thoracic and pelvic underpadding increases contact site pressure, decreases thoracic compliance, and increases pleural pressure [124]. In contrast, many experienced centres in Germany use special positioning materials in the performance of prone positioning. Whether the use of positioning aids to perform prone positioning supports and improves the effects of prone positioning therapy described above - homogenization of lung ventilation and improvement of the ventilation-perfusion ratio - or reduces negative consequences such as skin damage (intertrigo or pressure sores) cannot be answered at present based on scientific knowledge.

5 Mobilisation

Mobilisation includes measures on patients that initiate or support passive or active movement exercises and aim to promote or maintain the ability to move [125-130].

5.1 Clinical question: When should (early) mobilisation be started in the ICU?

At admission to the ICU or immediately after that, patients present with the highest severity of illness. Electrophysiological changes typical of critical illness myopathy are known to occur within 48 hours of ICU admission [131]. On day five, muscle is increasingly degraded and decreasingly built through dysregulation of the according systems [131, 132]. On day seven, 12.5% of the muscle mass of a patient is lost [133, 134]; mobilisation is the only treatment for which there is a proven therapeutic benefit in terms of preventing these pathophysiological changes in the neuromuscular system [135, 136]. At the same time, patients are least stable in this phase of illness and thus most susceptible to potential complications. This raises the question of the best time to start mobilisation to achieve the maximum therapeutic effect with the minimum risk.

In a network meta-analysis by Ding et al., the risk of ICU-acquired weakness (ICUAW) was lowest when mobilisation was started between 72 and 96 hours after the start of ventilation. In addition, the duration of ventilation was shorter when mobilisation was started between 48 and 72 hours compared with an earlier or later onset. The most unfavourable outcome regarding ventilation duration was the late start of mobilisation after more than five days of ICU stay. No influence of the start of mobilisation on ICU length of stay could be demonstrated. The area under the cumulative ranking curve indicated the best treatment outcome in terms of ICUAW as well as the duration of ventilation, with a mobilisation start between 48-72 hours after the start of ventilation [137].

In RCTs, it is evident that studies with the early start of mobilisation positively affected treatment outcomes. Schweickert et al. started mobilisation and daily awakening trials within 72 hours after the start of ventilation. They found a favourable effect on functional independence, delirium duration and ventilator-free days [135]. Similarly, Schaller et al. included ICU patients within 48 h of the start of ventilation. They showed a favourable effect

on functional independence, mobility, ICU and hospital length of stay, days without delirium and discharge home [136]. The RCTs by Wright et al. and Moss et al. with the start of mobilisation at five and seven days, respectively, could not show any advantage of the intervention on outcomes [138, 139].

The term “early mobilisation” is used in available studies without a uniform definition of the period between admission to the ICU or the start of ventilation and the beginning of mobilisation. In a systematic review from 2019, including 76 studies, 15 clearly defined early mobilisation, and another 15 at least partially defined it. A broad range, from mobilisation, starting 24 hours after admission to any time during the ICU stay, was referred to as early mobilisation [140]. In some cases, clinical parameters were used to determine the start of mobilisation. The PADIS guideline, for example, recommends the start of mobilisation when patients are stable in terms of their cardiovascular, respiratory and neurological status. The required values are explicitly based on expert opinions, as no primary data are available on these questions [141].

Given the beneficial effect of starting mobilisation within 72 hours, early mobilisation is defined as such in this guideline.

5.1.1 Definition of early mobilisation

Early mobilisation is defined as the start of mobilisation within 72 hours after admission to the ICU.

Recommendation 3.1 (modified 2022)
We recommend starting mobilisation of ICU patients within 72 h of admission.
Level of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: In general: LoE 1: Ding *et al.* [137]; Monsees *et al.* [142] LoE 2: Dong *et al.* [143]; Morris *et al.* [144]; Schaller *et al.* [136]; Schujmann *et al.* [145]; Schweickert *et al.* [135]; Zhou *et al.* [146] CABG/cardiac: LoE 2: Afxonidis *et al.* [147]; Cui *et al.* [148]; Ohbe *et al.* [149] Septic shock: LoE 2: Hickmann *et al.* [150] COPD: LoE 4: Chou *et al.* [151] Trauma: LoE 4: Coles *et al.* [152]; Elkbuli *et al.* [153]

5.2 Clinical question: What are the requirements to perform (early) mobilisation)?

An international survey of 951 ICUs revealed that barriers to early mobilisation exist even in ICUs that have established a mobilisation protocol and regularly perform (early) mobilisation. According to the survey, these barriers are mostly staff, lack of equipment and insufficient financial support [154]. A review of existing literature by Dubb et al. found that 70% of studies reported structural barriers [155]. A recent paper supports these findings [156]. It is, therefore, up to the hospital operator to create the necessary staff and material conditions to implement the recommendations of this guideline.

Active mobilisation of intensive care patients is a remarkably complex procedure, as they require direct support due to their physical weakness and indirect support in terms of monitoring due to catheters and ongoing additional treatments. This is especially true if active mobilisation occurs outside the bed. More time may be required to prepare the mobilisation session for complex patients with many cables and tubes for monitoring and therapy [157].

(Early) mobilisation is not a task of physiotherapists alone but of the entire treatment team to implement a training and mobilisation plan coordinated by the therapists with the other professional groups.

Recommendation 3.2 (new 2022)
We recommend that the hospital operator provides the personnel and material conditions to enable (early) mobilisation in line with these recommendations.
Level of recommendation: strong
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 95%; professional societies 91%.
Literature: [-]

5.3 Clinical question: Which patients should receive (early) mobilisation?

5.3.1 Patients who were previously functionally independent

Early mobilisation and mobilisation are interventions that, with a few exceptions, should be carried out in all critically ill patients because they compensate for the primarily ICU-specific immobilisation. It is the responsibility of the treatment team to discuss this task as part of the prioritisation of activities and to implement it as a team.

However, most studies exclude patients who were not previously functionally independent. For this reason, the evidence in the two patient groups is presented separately.

Klem et al. showed in a meta-analysis that ventilated patients benefit from (early) mobilisation in terms of duration of ventilation and ICU LOS. Their analysis only considered studies with a low or moderate risk of bias. [158]. Worraphan et al. confirmed the effect of (early) mobilisation on the duration of ventilation in a similar study cohort [159]. In a meta-analysis by Wang et al. that included patients regardless of their need for invasive mechanical ventilation, early mobilisation resulted in improved muscle strength (measured by Medical Research Council (MRC) score) in addition to shorter duration of ventilation, ICU and hospital LOS [160, 161], and better functionality (Barthel index) [162]. Anekwe et al. confirmed the improved muscle strength in a meta-analysis [163].

In a systematic review with meta-analysis by Waldauf et al., including critically ill patients regardless of mechanical ventilation, a shorter duration of ventilation and ICU LOS was found. In contrast, no effect on ICU and hospital mortality was demonstrated [164].

In contrast to most other studies, Okada et al. did not demonstrate an effect of (early) mobilisation on ICU length of stay, mortality, quality of life and functionality. At the same time, a shorter hospital LOS and improved muscle strength were shown [165].

Zhang et al. conducted a systematic review with meta-analysis on (early) mobilisation using the initiation criteria for early mobilisation of the PADIS guideline. The effects of (early) mobilisation were heterogeneous for the outcomes of muscle strength (MRC score, hand or quadriceps strength) and duration of ventilation. There was no effect on mortality at different time points. However, the probability of discharge home could be increased by (early) mobilisation [166].

The meta-analysis by Zang et al. demonstrated a beneficial effect of (early) mobilisation on the incidence of ICUAW, functionality (Barthel index), muscle strength (MRC score), as well as ICU and hospital LOS. At the same time, there was no effect on mortality and ventilator-free days [167].

The meta-analysis by Tipping et al. analysed predefined subgroup analyses for onset (early: ≤ 72 h versus late: > 72 h) and dose (short: < 30 min per day versus long: ≥ 30 min per day) of mobilisation analysing the long-term outcome days alive and out of the hospital to 180 days. Muscle strength was improved by (early) mobilisation regardless of subgroups. However, the ability to participate in activities of daily living was only improved by the higher mobilisation dose. Mortality was not reduced in any subgroup. Additionally, patients receiving (early) mobilisation experience more days alive and out of hospital (mean difference 9.7, 95% CI 1.7-17.7) [168].

Wang et al. used a similar approach and additionally considered the dose of (early) mobilisation in the control group. Consequently, the intervention reduced hospital and ICU LOS compared to the control. In contrast, the duration of ventilation was only shortened compared with patients receiving low-dose mobilisation in the control group. There was no effect on mortality, quality of life, or muscle strength; at best, there was a slight advantage for physical function [169].

In addition to acute treatment outcomes, long-term treatment outcomes are highly relevant for ICU patients. The post-intensive care syndrome (PICS) is a condition defined by limitations

in physical, cognitive, and mental health [170]. In a systematic review, Fuke et al. addressed whether (early) mobilisation influences PICS. They demonstrated improved muscle strength (MRC score) but no change in cognitive function or mental health but had to limit their statement due to the small number of studies on PICS [171]. The first indications of positive effects on depression, anxiety and post-traumatic stress disorder were shown in the work of Watanabe et al. [172].

Most meta-analyses were heterogeneous regarding the treatment outcomes studied (Table 1), likely because of different inclusion criteria, study designs, search periods and intervention definitions. Nevertheless, positive effects, primarily on ventilation and length of stay, were found in many meta-analyses, which is why (early) mobilisation must be recommended in patients without contraindications.

Most primary studies excluded patients who were functionally dependent or had significant physical limitations before ICU admission. There is no clear definition of functional dependence. Still, it is most commonly considered a condition where patients require assistance to walk or cannot perform activities of daily living independently [129]. Therefore, this group of patients must be assessed separately (see 5.3.2) and the general recommendation for (early) mobilisation must be limited to patients who are functionally independent before ICU admission [135, 139, 144-146, 173, 174].

Table 1. Treatment outcomes of (early) mobilisation in meta-analyses.

Systematic Review	LoE	Outcomes													
		Mortality		Physical Function	ICUAW	Muscle force*	Grip strength	Quality of life	Deliriu m	Safety	Duration of ventilation	ICU length of stay	Hosp. length of stay	Discharge home	others
		ICU	Hosp.												
Klem *et al.* [158]	1	n/a	○	n/a	n/a	n/a	n/a	n/a	n/a	✚	✚	✚	○	n/a	n/a
Worraphan *et al.* [159]	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	✚	n/a	n/a	n/a	○ 8
Wang *et al.* [162]	1	○	○	✚ 2	✚	✚	○	n/a	○	n/a	✚	✚	✚	n/a	✚ 9-11
Waldauf *et al.* [164]	1	○	n/a	○ 1	n/a	n/a	n/a	n/a	n/a	n/a	✚	✚	○	n/a	n/a
Anekwe *et al.* [163]	1	○		n/a	✚	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	✚	n/a
Okada *et al.* [165]	1	n/a	○	✚ 1	n/a	✚	○	○ 5, 6	n/a	n/a	n/a	○	✚	n/a	n/a
Zhang *et al.* [166]	1	n/a	n/a	n/a	✚	n/a	○	n/a	n/a	n/a	○ / ✚ 7	n/a	n/a	✚	○ 4
Zang *et al.* [167]	1	○	n/a	✚ 2	✚	✚	○	n/a	n/a	n/a	○ 7	✚	✚	n/a	✚ 9-11
Fuke *et al.* [171]	2	n/a	n/a	n/a	✚	✚	n/a	○ 5	○	n/a	n/a	n/a	n/a	n/a	n/a
Tipping *et al.* [168]	1	n/a	○	n/a	n/a	✚	n/a	○ 6	n/a	n/a	n/a	○	n/a	n/a	✚ 12, 13
Wang *et al.* [169]	1	○		✚ 2, 3	n/a	○	n/a	○ 6	n/a	n/a	○ / ✚ 14	✚	✚	n/a	n/a

✚ Positive effect; ○ No Effect; ▬ Negative effect

* measured by MRC Score; Abbreviations: ICU: Intensive Care Unit; Hosp: Hospital; LoE: Level of Evidence; ICUAW: Intensive Care Unit Acquired Weakness.

1: SF 36 Physical Component Score, 2: Barthel Index Score, 3: Functional Independence Measure 4: Quadriceps Strength, 5: EQ5D Score, 6: SF 36 7: ventilator-free days, 8: weaning duration, 9: ventilator-associated pneumonia, 10: deep vein thrombosis, 11: pressure ulcers, 12: probability of being independent walking at discharge home, 13: days alive and out of hospital on day 180, 14: positive effect of low-dose rehabilitation in the control group (!) and for functional intervention. No effect for high-dose physical rehabilitation in the control group or non-functional intervention.

Recommendation 3.3 (modified 2022)
We recommend the implementation of (early) mobilisation in all critically ill patients who were previously functionally independent and for whom there are no contraindications.
Grade of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: In general: LoE 1: Klem *et al.* [158]; Menges *et al.* [175]; Worraphan *et al.* [159]; Wang *et al.* [162]; Waldauf *et al.* [164]; Anekwe *et al.* [163]; Okada *et al.* [165]; Zhang *et al.* [166]; Zang *et al.* [167]; Tipping *et al.* [168]; Wang *et al.* [169]; LoE 2: Liang *et al.* [176]; Schujmann *et al.* [145]; Schaller *et al.* [136]; Morris *et al.* [144]; Schweickert *et al.* [135]; Zhou *et al.* [146]; Fuke *et al.* [171] CABG: LoE 3: Ribeiro *et al.* [177]; Dong *et al.* [178] cardiac: LoE 3: Nakamura *et al.* [179] Neurocritical Care: LoE 3: Schaller *et al.* [180]; LoE 4: Pang *et al.* [181]; Bahouth *et al.* [182]; Klein *et al.* [183] Septic shock: LoE 2: Hickmann *et al.* [150] Liver transplant: LoE 3: Maffei *et al.* [184] Trauma: LoE 3: Higgins *et al.* [185]; LoE 4: Coles *et al.* [152] No Effect: LoE 3: Moss *et al.* [139]

5.3.2 Patients who were not previously functionally independent

There are currently no studies explicitly investigating patients with functional dependence before the ICU, but only those that did not explicitly exclude these patients.

Two prospective randomised controlled trials, including patients ≥ 60 years after cardiac surgery or in septic shock, have shown that (early) mobilisation reduces hospital length of stay and improves health-related quality of life [148, 186]. This is complemented by the retrospective cohort study by Yagi et al., which demonstrated lower mortality and higher weaning rates in a matched cohort through (early) mobilisation, even for previously dependent patients [187]. Similarly, the non-randomised controlled study by Gatty et al. shows that (early) mobilisation increases the level of mobilisation on the last day of rehabilitation even in previously functionally dependent patients [188].

Other studies with a low level of evidence examined cohorts with surrogates for functional dependence. Kim et al. compared the effect of (early) mobilisation in a case-control study in patients with low and normal muscle mass and showed that (early) mobilisation has a beneficial impact on in-hospital and six-month mortality only in patients with low muscle mass [189].

The before-and-after study by Goldfarb et al. investigated the effectiveness of implementing an (early) mobilisation protocol in patients ≥ 80 years of age in a cardiac intensive care unit. The authors describe that 38% had a functional limitation before admission. Establishing the protocol reduced hospital mortality and increased the proportion of all patients who could be discharged home [190]. The retrospective cohort study by Goldfarb et al. is one of the few studies that investigates the influence of functional status before admission on the effectiveness of (early) mobilisation. Functional status was quantified using the Rockwood Clinical Frailty Scale. Frailty was found to not influence the change in functionality in the perioperative context [191].

Fuest et al. confirmed through multivariate analyses in a matched cohort that frail patients do not deteriorate functionally more frequently than non-frail patients. Even if ground effects of the functional test variable must be considered, it indicates that efforts should also be made in this patient group to at least maintain the functional status [192].

Given the available evidence, there are no studies with a high level of evidence to support the effect of (early) mobilisation in patients who were functionally dependent prior to ICU admission. Nevertheless, based on the studies for frail patients, elderly patients, and patients with low muscle mass, as well as studies that do not exclude based on functional dependence, the inclusion of these patients in (early) mobilisation programmes is formulated as a weak recommendation.

Recommendation 3.4 (modified 2022)
We suggest performing early mobilisation in critically ill patients who were functionally dependent prior to ICU admission and for whom there are no contraindications.
(Early) mobilisation.
Grade of recommendation: weak
Level of evidence: 3
Literature: In general: LoE 3: Yagi *et al.* [187], Gatty *et al.* [188]; Thiolliere *et al.* [193]; LoE 4: Iwai *et al.* [194] Sepsis: LoE 3: Kayambu *et al.* [186]; LoE 4: Kim *et al.* [189], Liu *et al.* [195] Cardiac/Heart surgery: LoE 2: Cui *et al.* [148]; Borges *et al.* [196];LoE 3: Cordeiro *et al.* [197] Neurocritical Care: LoE 3: Bartolo *et al.* [198]; LoE 4: Bartolo *et al.* [199]; Kim *et al.* [200] Trauma: LoE 4: Booth *et al.* [201]; Coles *et al.* [152]; Elkbuli *et al.* [153] Burns: LoE 4: Deng *et al.* [202]; O'Neil *et al.* [203]

5.3.3 Patients with continuous renal replacement therapy

Possible dislocation of intravascular catheters is a common barrier to (early) mobilisation. Continuous renal replacement therapy (CRRT) requires catheters that are large in volume, which may, if dislocated, lead to significant blood loss.

Mayer et al. specifically addressed the safety of (early) mobilisation in the context of continuous renal replacement therapy and analysed 15 included studies with a cumulative of 436 patients mobilised during CRRT in a systematic review. In ten studies with 840 mobilisation units, a total of 15 (1.8%) adverse events were reported, two of which were serious (disconnection of CRRT catheter, hypotension requiring catecholamines) [204].

An observational study by Toonstra et al. included 57 patients with at least one mobilisation session during CRRT. Six adverse events (mean arterial pressure < 55 mmHg) and no serious adverse events occurred during a total of 268 mobilisation sessions, which were mobilised up to walking [205]. Results of studies with smaller cohorts or lower evidence also coincide with these results [206-209].

The available evidence shows the safety of (early) mobilisation in the context of CRRT, which is why it should not be considered a contraindication.

Recommendation 3.5 (new 2022)
We recommend mobilising patients on continuous renal replacement therapy (CRRT).
Grade of recommendation: strong
Level of evidence: 2
Consensus strength: guideline members 94%; professional societies 91%.
Literature: LoE 2: Mayer *et al.* [204]

5.3.4 Patients with subarachnoid haemorrhage or external ventricular drains

Neurological and neurosurgical patients need to be considered separately concerning mobilisation, as they are potentially more prone to develop adverse effects associated with (early) mobilisation. These include alterations in intracranial pressure and blood flow (vasospasm), which can lead to significantly increased morbidity in patients with subarachnoid haemorrhage (SAH) and external ventricular drain (EVD). A milestone in this regard was the large before-and-after study published by Titsworth et al. All neuro-intensive care patients were consecutively included in the intervention phase of the study, which included diagnosis of SAH (20%), malignancy (20%), stroke (19%), intracerebral haemorrhage (8%) or subdural hematoma (8%). Results showed that the mobilisation concept was safe, increased mobility, reduced the VAP rate and ICU and hospital LOS [210]. These findings were confirmed by Bartolo et al. in patients with severe acquired brain injury (both traumatic and non-traumatic) [199]. It should be noted that there is evidence from stroke research (i.e. stroke units and not intensive care units) that mobilisation started very early (< 24h) can be harmful for patients [211]. In particular, performing several short mobilisation sessions instead of one long session seems vital [212]. The S2e guideline on acute therapy of ischaemic stroke (AWMF register number 030-046, version 2021) recommends, "All stroke patients should start mobilisation (out-of-bed activity) within 48 hours of stroke onset. Grade ↑, LoE 2" [213]. However, it is unknown to what extent these findings can be applied to ICU patients with stroke.

Despite the available literature, bed rest remained an integral part of treating patients with SAB or EVD in many hospitals [198]. The 2013 Cochrane Review noted that no controlled trials provided evidence for or against bed rest for at least four weeks after the onset of symptoms in patients with aneurysmal SAH [214].

In recent years, the first observational studies have been published describing the adverse effects of (early) mobilisation in SAB and analysing desirable effects on treatment outcomes. Young et al. studied the two phases of implementing an early mobilisation programme for patients with SAB and EVD. No mobilisation was carried out prior to the programme. In the first phase, early mobilisation was performed by therapists only and included sitting on the edge of the bed, standing, and stepping in place. In the second phase, mobilisation measures were expanded qualitatively (sitting in a chair outside the bed), quantitatively (up to 3 hours a day) and in terms of personnel (mobilisation provided by nursing staff). Due to the addition of nursing staff, the patients were mobilised more frequently and longer, but not earlier; all patients could be discharged to home care or rehabilitation centres. LOS and ventilation days significantly improved in the first phase. Due to pain, hypotension or increased intracranial pressure, 12% of the mobilisation sessions were discontinued [215].

In the retrospective analysis by Yataco et al., 117 of 153 patients with EVD were mobilised. The highest level of mobilisation achieved was walking. This level of mobilisation was completed by 51 patients. Adverse events such as nausea, headache and vomiting occurred in 6.9% of patients. Still, there was no dislocation of an EVD, so the study's authors considered the early mobilisation of patients with EVD feasible [216].

Shah et al. came to the same conclusion in their prospective case series on early mobilisation of patients with EVD. In 90 patients with 185 mobilisation sessions, only four (2.2%) adverse events occurred (increased intracranial pressure, vomiting and dislocation of an EVD). The level of mobilisation achieved included active standing in 81% of the mobilisation sessions. However, only patients who met the following criteria were mobilised: Lindegaard ratio < 3.0, mean flow velocity in the middle cerebral artery < 120 cm/s, mean arterial pressure > 80 mmHg and constant intracranial pressure < 20 mmHg [217].

The retrospective cost analysis by Hester et al. in a neuro-ICU showed that implementation of an early mobilisation protocol reduces ICU and hospital LOS, reduces costs immediately after implementation of the protocol and has no adverse events [218]. A similar positive outcome after implementing a mobilisation protocol - this time in terms of functionality on transfer from the ICU - was shown in another retrospective study in patients with intracranial or subarachnoid haemorrhage [219].

In the prospective interventional study by Karic et al., patients with aneurysmal SAB in an intermediate care unit (i.e., non-ventilated patients) were studied, with 77 patients treated in 2011 receiving standard therapy and 94 patients treated in 2012 receiving early mobilisation. The early mobilisation protocol resulted in an earlier onset of mobilisation and mobilisation to a higher level. Patients in the intervention group had significantly later and fewer clinical vasospasms. There were also no increased complications in the intervention group [220]. At one-year follow-up, the neurological outcome was better after early mobilisation (Modified Rankin Scale, Glasgow Outcome Scale), but only in patients with poor neurological status on admission to the ICU [221].

Early mobilisation in patients with SAB and EVD appears feasible but with the risk of intracranial pressure elevations and ventricular drain dislocations. The beneficial effects are consistent with those of early mobilisation in other cohorts. However, the evidence is limited, and RCTs in these patient cohorts are very much needed. Currently, we can only suggest mobilisation under close interdisciplinary consultation and strict risk-benefit assessment.

Recommendation 3.6 (new 2022)
We suggest mobilising patients with subarachnoid haemorrhage or external ventricular drainage after interdisciplinary consultation, considering potential risks and benefits.
Grade of recommendation: weak
Level of evidence: 3
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 3: Bartolo *et al.* [198], Titsworth *et al.* [210] LoE 4: Bartolo *et al.* [199]; Young *et al.* [215]; Yataco *et al.* [216]; Shah *et al.* [217]; Hester *et al.* [218]; Karic *et al.* [220]; Karic *et al.* [221]; Rand *et al.* [219]; Olkowski *et al.* [222]

5.3.5 Patients with ECMO-/ECLS therapy

ECMO therapy is only used in critically ill patients. Accordingly, the most common predefined barriers to (early) mobilisation apply to these patients, such as sedation, haemodynamic or respiratory instability, and dislocation of a medical device, particularly the acutely vital ECMO cannula.

Braune et al. investigated whether mobilisation is feasible and safe in patients receiving extracorporeal life support (ECLS) therapy. In their observational study, 43 of 115 patients (37%) with ECLS therapy - including ECMO - could be mobilised to a mobilisation level ≥ 3 on

the ICU Mobility Scale (IMS), which corresponds to sitting at the edge of the bed. Mobilisation was possible on 310 of 1242 (24.9%) ECLS days, with the most common reasons for withholding mobilisation being sedation, poor general condition, lack of staff and haemodynamic or respiratory instability. Low blood flow alarms occurred in 3.4% of mobilisations and critically low blood flow alarms in 1.2%, always lasting < 60 seconds. Other adverse events were desaturation (SpO2 < 85%) in 19% of mobilisation sessions, hypotension (MAP < 50 mmHg) in 7.5% of mobilisations, and tachycardia (> 140 beats per minute) in 5.7% of mobilisations. All adverse events were self-limiting or could be resolved by the treatment team. Relevant bleeding (requiring discontinuation of mobilisation, surgical intervention, or transfusion) occurred in 6.9% of actively mobilised patients and 15.3% of non-actively mobilised patients. Dislocation of the ECMO cannula occurred during one mobilisation (0.3% of mobilisations), though immediate recannulation was possible [223]. Another small retrospective study also indicated that mobilisation during ECMO therapy was more likely to have adverse events [224], while in other retrospective studies, only 0-2 % adverse events occurred during mobilisation under ECMO [225-227].

A first prospective randomised controlled trial from 2020 investigated the feasibility and safety of mobilisation under ECMO therapy. A total of 20 patients were randomised to the intervention group (early mobilisation for seven days) or the control group (standard of care) within 72 hours of the start of ECMO therapy. In total, only five patients were mobilised, four in the intervention group and one in the control group, which is why the study has a pilot character due to the lack of statistical power [228]. In a secondary analysis, no difference in respiratory or haemodynamic parameters could be found. No adjustment of ECMO therapy settings was necessary in this sub-cohort, and no adverse events occurred. The patients in the intervention group could be mobilised to standing significantly earlier [229].

In the observational study by Liu et al., all patients with an unplanned ICU admission were included over twelve months and mobilised according to the newly established mobilisation protocol. Of the 232 critically ill patients included, six patients under ECMO therapy had 110 mobilisation units with only four unspecified adverse events but no dislocation of an ECMO cannula [230].

Patients with ongoing ECMO therapy are a high-risk cohort, but (early) mobilisation is generally very safe. With appropriate experience and preparation, (early) mobilisation should also be performed in ECMO patients because of the expected treatment benefit. In this context, it should be remembered that ECMO therapy should only be performed in specialised centres [231]. This also applies to the (early) mobilisation of these patients [228].

Recommendation 3.7 (new 2022)
We recommend performing (early) mobilisation during ECMO therapy.
Grade of recommendation: strong
Level of evidence: 3
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 3: Braune *et al.* [223]; ECMO PT Study Investigators [228]; Liu *et al.* [230]

5.3.6 Everybody who is not explicitly excluded

Immobilisation has far-reaching negative consequences for healthy subjects and especially for the seriously ill. In healthy individuals immobilised for 70 days, there is a loss of up to 0.33% of muscle mass per day [232]. In addition, muscle strength and neuromuscular function deteriorate in healthy subjects, which cannot be fully explained by atrophy [233]. Insulin resistance presents within seven days of immobilisation [234]. Besides immobilisation, inflammation also proved to be a complicating factor [132, 235, 236], with immobilisation presenting as an essential complicating factor in muscle recovery in animal models [237].

Despite the proven negative impacts of immobilisation, international prevalence studies demonstrate that ICUs do not meet the recommended mobilisation goals [154, 238-240]. It is, therefore, essential to implement the recommendations provided by national and international guidelines in the daily routine of the entire treatment team to promote (early) mobilisation as the standard of care. Specialist nurses or physiotherapists should independently initiate and coordinate mobilisation measures according to an individual risk-benefit assessment and based on local protocols if there is no medically required immobilisation. Importantly, immobilisation requires an explicit prescription and justification (see Chapter 5.4) [241].

Recommendation 3.8 (new 2022)
We recommend an explicit prescription of medically required immobilisation.
Level of recommendation: strong
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: Aquim *et al.* [242], Devlin *et al.* [141], Murray [243]

5.4 Clinical question: Which patients should not receive (early) mobilisation?

In addition to its effects on functionality and muscle mass, (early) mobilisation prevents contractures even by passively mobilising the joints. Passive mobilisation does not generally impact the muscular, cardiovascular, or respiratory system. During active mobilisation, increased muscular metabolism and activation of the cardiovascular and respiratory systems are intentional, and moderate desaturation or hypotension are therefore expected [136]. Respiratory and cardiovascular reserve, therefore, need to be assessed before active mobilisation to adapt its intensity adequately. There is currently no evidence that supports absolute parameters as contraindications for mobilisation, emphasising the importance of the overall clinical presentation of an individual patient. The values presented in the guideline are based on expert opinions and mobilisation protocols published in the current literature, which may support individual risk-benefit assessment (see Table 2).

Table 2. Safety criteria for starting mobilisation

Parameter	Limit value suggested by the guideline members	Limit values in studies	Reference
Blood glucose (mg/dl)	> 50	> 50	Wahab *et al.* [244]
Systolic blood pressure (mmHg)	70-180	< 200	Wahab *et al.* [244]
		< 180	Conceicao *et al.* [245]
		< 170	Aquim *et al.* [242]
		65 - 180	Sakai *et al.* [246]
		90 - 200	Yang *et al.* [247]
Mean arterial blood pressure (mmHg)	60-115	< 110	Sakai *et al.* [246]
		65 - 110	Yang *et al.* [247]
		60-110	Sommers *et al.* [248]
		60 – 115	Fraser *et al.* [249]
		> 60	McWilliams *et al.* [250]
		> 55	Wahab *et al.* [244]
		55-140	AHRQ Safety Program for Mechanically Ventilated Patients [251]
Heart rate (min^{-1})	40-120	40-130	Yang *et al.* [247] Sakai *et al.* [246] Conceicao *et al.* [245] Wahab *et al.* [244] Sommers *et al.* [248]
		< 120	Hodgson *et al.* [252]
		50-120	Fraser *et al.* [249]
		≤ 150 and absence of bradyarrhythmia requiring pharmacologic treatment	Presneill *et al.* [253]
Vasopressors	Equivalent to ≤ 0.2 µg/kg/min noradrenaline	< 0.1 µg kg^{-1} min^{-1} noradrenaline or adrenaline < 10 µg kg^{-1} min^{-1} dopamine	Sommers *et al.* [248]
		< 0.2 µg kg^{-1} min^{-1} noradrenalin or equivalent	McWilliams *et al.* [250]
		≤ 0.2 µg kg^{-1} min^{-1} or < 0.1 µg kg^{-1} min^{-1} if increase of noradrenalin/adrenalin-rate > 25% in the last 6 hours	Presneill *et al.* [253]
Oxygen saturation (%)	≥ 88	> 90	Aquim *et al.* [242] Hodgson *et al.* [252] Sommers *et al.* [248]
		≥ 88	Yang *et al.* [247] Sakai *et al.* [246] Wahab *et. al.* [244] AHRQ Safety Program for Mechanically Ventilated Patients [251]
		≥ 86	Fraser *et al.* [249]

PEEP (cmH2O)	**≤ 12 (except obese patients)**	**≤ 12**	**Fraser *et al.* [249] McWilliams *et al.* [250]**
		≤ 10	Hodgson *et al.* [252] Yang *et al.* [247] AHRQ Safety Program for Mechanically Ventilated Patients [251] Sommers *et al.* [248]
		≤ 10 for mobilisation level above sitting on the edge of the bed	McWilliams *et al.* [250]
		≤ 16	Presneill *et al.* [253]
F_iO_2	≤ 0.6	< 0.6	McWilliams *et al.* [250] AHRQ Safety Program for Mechanically Ventilated Patients [251] Sommers *et al.* [248]
		≤ 0.6	Presneill *et al.* [253]
Respiratory rate (min^{-1})	5-40	5-40	Yang *et al.* [247] Sakai *et al.* [246] Fraser *et al.* [249] Wahab *et al.* [244]
		< 35	AHRQ Safety Program for Mechanically Ventilated Patients [251]
		≤ 40	Sommers *et al.* [248]
		≤ 45	Presneill *et al.* [253]
Lactate	-	≤ 4.0 mmol/L	Presneill *et al.* [253]
Cardiac index	-	≥ 2.0 L/min/m^2	Presneill *et al.* [253]
Temperature	36.0 °C – 38.5 °C	36.0 °C – 38.5 °C	Sommers *et al.* [248]

All criteria and values listed in Table 2 do not replace the treatment team's individual assessment of the critically ill patient.

Recommendation 3.9 (modified 2022)
We recommend mobilisation in patients with adequate respiratory and cardiovascular reserve. However, we are currently unable to make an evidence-based recommendation on absolute values that are considered a contraindication to mobilisation.
Grade of recommendation: strong
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Aquim *et al.* [242]; Wahab *et al.* [244]; Conceicao *et al.* [245]; Sakai *et al.* [246]; Yang *et al.* [247]; Fraser *et al.* [249]; McWilliams *et al.* [250]; AHRQ Safety Program for Mechanically Ventilated Patients [251]; Hodgson *et al.* [252]; Presneill *et al.* [253]; Boyd *et al.* [254]

5.5 Clinical question: When should a mobilisation session be discontinued or aborted?

The reviews by Nydahl et al. show 2.6 - 3.9% adverse events and 0.3 - 0.6% serious adverse events during mobilisation of critically ill patients [255, 256]. Consequently, close monitoring during a mobilisation session is essential to detect changes requiring discontinuation early on. Reference values are desaturation < 86%, an increase of heart rate > 30% of baseline, an increase in systolic blood pressure ≥ 40 mmHg or diastolic blood pressure ≥ 20 mmHg, new or increased cardiac arrhythmias and a deterioration of the level of consciousness [246]. Suppose the treatment team concludes that mobilisation cannot be conducted or continued at the time of assessment due to a limited respiratory and cardiovascular reserve, therapeutic measures should be taken to improve the patient's condition and enable mobilisation [246].

All criteria and values listed here are intended as a reference without general validity and do not replace the individual assessment of the patient.

Recommendation 3.10 (modified 2022)
We suggest discontinuing a mobilisation session if according to judgement, it poses a risk to the patient. These criteria may be: - desaturation < 86% - heart rate increase > 30% from baseline - ystolic blood pressure rise ≥ 40 mmHg from baseline - diastolic blood pressure rise ≥ 20 mmHg from baseline - mean arterial pressure < 50 mmHg from baseline - new onset or worsened cardiac arrhythmia requiring treatment - deterioration of the level of consciousness compared to the start
Grade of recommendation: weak
Level of evidence: 5 (expert opinion)
Consensus strength: guideline members 94%; professional societies 100%
Literature: LoE 4: Sakai *et al.* [246]; Fraser *et al.* [249]

5.6 Clinical question: How should (early) mobilisation be performed?

5.6.1 Protocol-based (early) mobilisation of critically ill patients

Recently, it has been repeatedly shown that implementing (early) mobilisation in the ICU does not reach the quality and quantity recommended by guidelines. In 2016, a survey of 951 ICUs showed that 48% of ICUs perform early mobilisation, and only 21% have established a protocol

[154]. The successful implementation of (early) mobilisation in everyday clinical practice requires interprofessional cooperation and coordination, which can be facilitated through a mobilisation protocol. Introducing a protocol leads to an earlier start of (early) mobilisation. Furthermore, the institutionalisation of early mobilisation can reduce financial, staff and equipment-related barriers [154]. In summary, protocols increase the feasibility and safety of (early) mobilisation treatment [257].

In a RCT by Schujmann et al., the application of a mobilisation protocol led to a significant increase in active time during hospitalisation with 4.18% in the control group compared to 7.55% in the intervention group. At discharge from the ICU, patients in the intervention group were significantly more functionally independent and achieved a higher mobilisation level. This result was also confirmed in the sit-to-stand and 2-minute walk tests. In addition, the mobilisation protocol led to a significantly shorter ICU stay [145].

In a randomised controlled pilot study from 2016, Hodgson et al. investigated a protocol based on active mobilisation, in which mobilisation was started at the highest possible level and decreased in level only if necessary. The aim was to spend as much time as possible at the highest possible mobilisation level. This approach contrasted with protocols starting with a slow increase in mobilisation intensity. As a result, patients in the intervention group achieved a higher mobilisation level by applying the protocol. Overall, 90% of the patients in the intervention group were standing, and 66% were mobilised to walk, compared to 62% and 38% in the control group, respectively. They also received longer mobilisation sessions [173].

The first international multicentre RCT applying a mobilisation protocol by Schaller et al. proved effective. 52% In the intervention group, compared with 25% in the control group, achieved the highest level of mobilisation at ICU discharge compared to the control group. The ICU LOS was shortened, and the physical function at ICU discharge was significantly improved [136].

The available evidence shows that a more (early) mobilisation in terms of duration and intensity can be achieved by applying a mobilisation protocol. All studies had a significant separation between the intervention and control groups. Scheffenbichler et al., Watanabe et al., and Paton et al. showed in their analyses that the mobilisation dose (duration and level) are relevant predictors for an improved treatment outcome [258-260]. This was confirmed by

the RCTs of Morris et al. and Schaller et al. [136, 144]. Accordingly, a protocol-based approach should be established when performing (early) mobilisation.

Recommendation 3.11 (modified 2022)
We recommend a protocol-based approach for implementing (early) mobilisation.
Level of recommendation: strong
Level of evidence: 1
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 1: Waldauf *et al.* [164] LoE 2: Schaller *et al.* [136]; Schujmann *et al.* [145]; Morris *et al.* [144]

5.6.2 Safety criteria for mobilisation

According to the subjects presented in Chapters 5.4, "Which patients should not receive (early) mobilisation?" and 5.5, "When should a mobilisation session be discontinued?" the integration of individual ICU-based safety criteria into mobilisation protocols is recommended.

Recommendation 3.12 (new 2022)
We suggest integrating safety criteria (e.g., pulmonary and cardiovascular conditions) into the mobilisation protocol.
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Schaller *et al.* [136]; Schujmann *et al.* [145]

5.7 Clinical question: How should a mobilisation session be prepared?

Mobilisation of ICU patients is a demanding treatment procedure that requires careful preparation and interprofessional coordination both within the treatment team and with the patient.

Once the daily mobilisation goal has been set, three aspects should be considered in addition to the patient during preparation: 1. the therapeutic measures to continue therapy during mobilisation; 3. the mobilisation equipment; 4. the safety measures. If the level of consciousness is adequate, patients should be involved in the planning of the mobilisation session. Additionally, sedation may have to be reduced. Preparation of intensive care therapy

measures may include extension of perfusion lines or ventilation tubes, disconnection from dialysis, and availability of additional material such as a mobile ventilator, oxygen cylinders or mobilisation aids (e.g., bed bicycle, walker). Preparation of safety measures includes adjusting the alarm values on the transport monitor and ventilator and providing additional staff to support the patient.

The measures listed here are only examples and cannot be applied to every situation without restrictions. It is vital to plan these aspects individually in the interprofessional team based on the clinical background of the critically ill patient.

Recommendation 3.13 (modified 2022)
For preparing a mobilisation session, we suggest - informing the patient, - providing sufficient staff, and - securing/extending artificial airways, IV lines or other drains. To monitor vital signs during mobilisation, heart rate, blood pressure and peripheral oxygen saturation should be recorded continuously / closely. In ventilated patients, the most important ventilation parameters should be continuously monitored.
Grade of recommendation: weak
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: [-]

5.7.1 Types of mobilisations

Mobilisation covers various interventions, from passive range of motion to walking outside the room. Different approaches to mobilisation are established in the literature.

Passive mobilisation only

Passive mobilisation is included as the lowest level in most mobilisation protocols, to be applied when the patient's consciousness, cognition or haemodynamics are so limited that active mobilisation cannot be performed [261-264]. Passive mobilisation benefits patients with impaired consciousness and stroke patients [180, 200, 264].

Rahiminezhad et al. investigated the effect of massage and range of motion exercises (passive/assisted/active) in addition to usual care in an RCT. The massage group received a daily massage for 30-60 minutes in addition to usual care, whereas the second group had ROM exercises for 30-60 minutes. The control group received usual care, which included respiratory

and limb physiotherapy. Results showed a significant increase in muscle strength in both intervention groups. Nevertheless, there was a more significant increase in strength with passive, assisted or active movement exercises for 30-60 minutes than in the group with a massage [265].

There is no evidence comparing active and passive mobilisation in critically ill patients. However, there is evidence that early implementation of passive mobilisation may be beneficial [200, 264, 266].

Passive and active mobilisation combined

Most mobilisation protocols contain passive and active mobilisation elements ranging from passive mobilisation to walking independently, which can be applied depending on the patient's condition during any phase of the disease [152, 182, 244, 249, 267, 268].

However, the various mobilisation protocols differ. For example, Sigler et al. proposed an eight-level, progressive model in which patients start sitting on the edge of the bed only on level five [268]. In a protocol for patients with intracranial haemorrhage, Bahouth et al. also considered mental status and motor function. If the patient is in a stable condition, active mobilisation is performed on eight different level, alternatively passive mobilisation is used (three levels if upper body elevation is possible, otherwise two levels) [182]. Furthermore, a rehabilitation pathway implemented the recommendations of the National Institute for Health and Care Excellence for rehabilitation management in the ICU. The level and duration of mobilisation were adapted to the patient’s clinical condition. Patients with significant functional impairments received either passive mobilisation, assisted mobilisation or measures to prevent respiratory complications. Patients with mild impairments, on the other hand, were gradually included in breathing exercises, muscle strength training, transfers, and walking. In this six-level approach, patients were mobilised between 20 and 45 minutes daily, six days per week [269]. A progressive mobilisation protocol that included four intervention levels was used by Fraser et al., where caregivers, care assistants and family members performed the first level of mobilisation without the mobility team [249].

Many scores, such as the Surgical ICU Optimal Mobilisation Score (SOMS) protocol, combine passive and active elements [180, 261-263]. The mobilisation goal of the SOMS was based on

the clinical condition of the patient and the level of mobilisation achieved on the previous day (Figure 3). The levels and according conditions are 0 - no mobilisation in the presence of an unstable spine or elevated ICP, 1 - passive movement exercises and elevated upper body if there is no indication for immobilisation, 2 - sitting, when the patient can move extremities and to follow simple commands, 3 - standing, with a strength level of at least 3 out of 5 and the ability to sit without support, and 4 - walking, as soon as patients can stand and walk on the spot with minimal support.

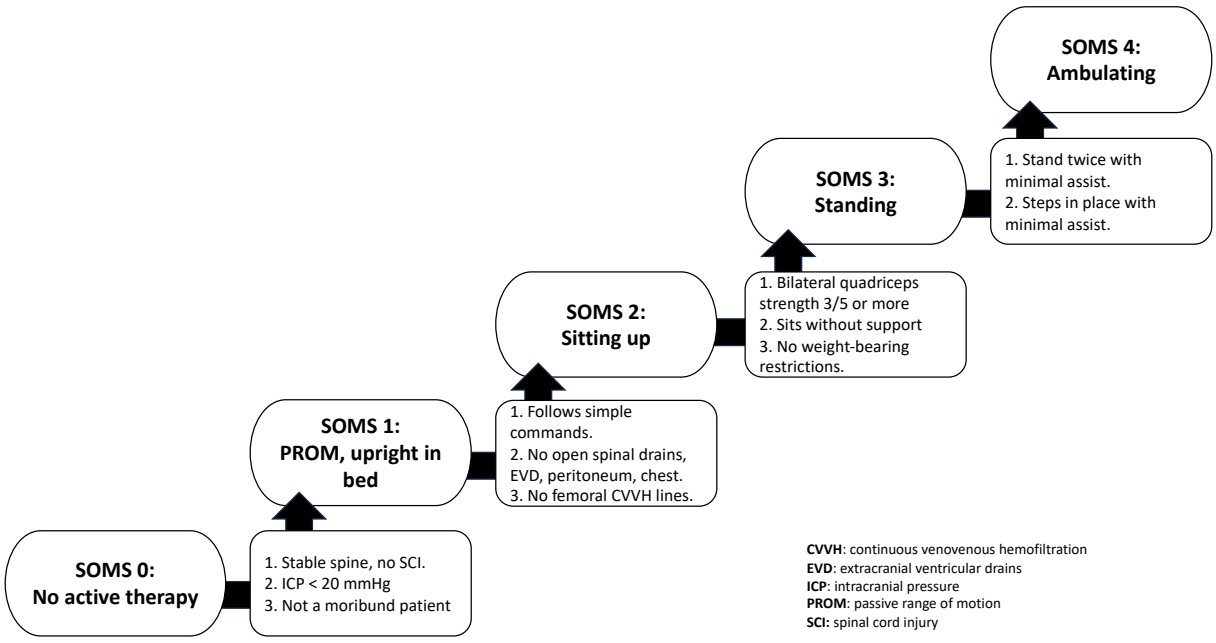

Figure 3. Surgical Optimal Mobility Score adapted from Meyer et al. [270]

Barriers to mobilisation were identified and discussed in the interdisciplinary team to effectively remove them and enable mobilisation. Applying the SOMS protocol in a multicentre randomised controlled intervention trial improved functionality and shortened ICU LOS [136].

Additional established mobilisation protocols based on similar concepts include the Manchester Protocol [250] or the protocol of the Early Mobilisation Network [271].

Early active mobilisation

Concepts focusing exclusively on active mobilisation exist. The IMS was developed by a multidisciplinary and interprofessional group of experts in the field of (early) mobilisation in intensive care in Australia. A patient's mobilisation goal is set daily based on the IMS and the clinical condition. In contrast to protocols with a slow increase in mobilisation intensity, each patient is mobilised to the highest possible level of mobilisation at the beginning, which is then reduced as needed, and the levels consist of only active mobilisation (Figure 4).

In a pilot study, applying the IMS protocol created a sufficient separation in mobilisation dose between the intervention and the control group [173]. The results of the TEAM RCT assessing patient-centred long-term endpoints could no longer be fully evaluated prior to the publication of this guideline [253, 272]. To date, the question of adequate dose remains unanswered [273]. There is no evidence to support the advantage of mobilisation protocols that only perform active mobilisation over mobilisation protocols that combine passive and active range of motion exercises. The clinical advantage of mobilisation protocols combining passive and active mobilisation is proven and recommended.

Recommendation 3.14 (new 2022)
We recommend using both passive and active components in the mobilisation protocol.
Level of recommendation: strong
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Schujmann *et al.* [145]; Schaller *et al.* [136]; Rahiminezhad *et al.* [265]

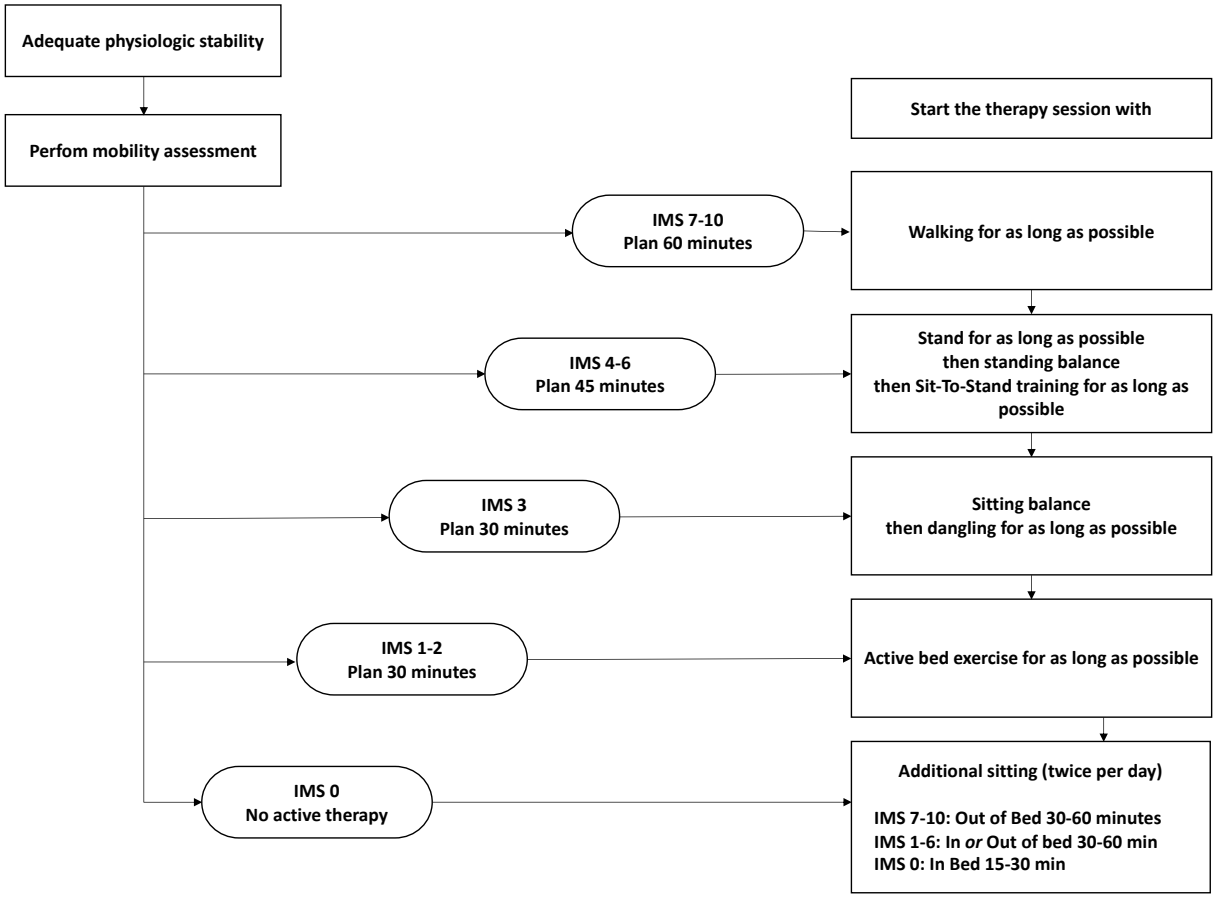

Figure 4. ICU Mobility Scale (IMS) adapted from Hodgson et al. [173]

5.8 Clinical question: How long and frequently should mobilisation be performed?

The choice of mobilisation dose remains relevant when using mobilisation protocols in everyday clinical practice. The dose consists of the duration, intensity (especially level) and frequency of mobilisation therapy. In the last version of the guidelines, expert consensus recommended mobilisation twice daily for at least 20 minutes each (i.e., at least 40 minutes per day) [274].

The IMS concept recommends even significantly longer daily mobilisation times (of active mobilisation) without a specification of the frequency (Table 3)[173].

Table 3. Timelines in the IMS concept [173, 275, 276]

IMS Level	Suggested mobilisation time (minutes)
10 - 7	60
6 - 4	45
3	30
2 - 1	30
0	15 - 30

Notably, the duration of mobilisation in RCTs is often much shorter. Patients in the pilot RCT performed by Hodgson et al. were mobilised daily for a mean duration of 20 minutes, while the control group received only seven minutes of mobilisation per day [173].

In the RCT by Wright et al., the mobilisation protocol was planned to be 90 minutes in the intervention group and 30 minutes in the control group; however, the two groups received only 23 minutes versus 13 minutes on mobilised days (57% vs. 40%), respectively [138].

In the multicentre randomised controlled intervention study by Schaller et al., patients were mobilised daily, and the mobilisation goal was achieved on 89% of the study days. The intervention led to a shortened ICU LOS and improved physical function at discharge. Mobilisation duration in the study cohort was low, averaging 60 minutes during the ICU stay [136].

In the RCT by Morris et al., patients in the intervention group were mobilised three times daily and showed improved physical function six months after discharge. However, mobilisation did not improve short-term outcomes [144].

The prospective, international cohort study by Scheffenbichler et al. directly addressed the influence of the mobilisation dose (level x time). Results indicated that a higher mobilisation dose reduced the risk of adverse discharge disposition and mortality, hospital and ICU LOS, and improved physical function. Furthermore, duration of mobilisation was independently associated with a reduced risk of adverse discharge [258].

So far, it has only been shown that a longer mobilisation duration is associated with a better overall treatment outcome, which is why the longest possible mobilisation should be carried out in a patient-adapted manner [258, 277, 278]. In addition, studies show a beneficial effect on daily mobilised patients, which is why it seems worthwhile.

In contrast, results from stroke research on stroke units (not ICUs) demonstrated a negative effect of earlier (within 24 h after admission) and more intense mobilisation [211]. In a predefined dose-response analysis of the same study, early onset and higher total duration had a negative impact. However, a higher frequency was beneficial for the same total duration, i.e., several short sessions throughout the day are preferable to one long session [212].

At present, no minimum or maximum duration or frequency of mobilisation can be recommended based on the available evidence, especially since it is to be expected that an individual dose will have to be found depending on the basic constitution of the patient as well as the current clinical condition. Further scientific research in this area is necessary.

Recommendation 3.15 (modified 2022)
We recommend daily mobilisation with sufficient duration.
Level of recommendation: strong
Level of evidence: 5 (expert recommendation)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: Guideline reference: Aquim *et al.* [242] LoE 2: Schaller *et al.* [136]; Morris *et al.* [144]; Dong *et al.* [143], Winkelmann *et al.* [278]

5.9 Clinical question: With what intensity should mobilisation be performed?

Based on the current literature, beneficial effects are limited if guideline-based (early) mobilisation is established as the standard of care [156, 279]. There are also signs and symptoms of excess physical burden [280], although exact limits are currently unknown [273].

In the observational study by Paton et al., 185 patients were followed up on their health status using the EQ-5D-5L six months following ICU admission. It was shown that a higher mobilisation level measured by the IMS during the ICU stay was associated with better health status, independent of sex and disease severity. In addition, patients who achieved an IMS ≥ 5 (transfer from bed to chair) showed a significantly better health status [259].

Raurell-Torredà et al. also conducted a multicentre observational study to identify predictors of ICUAW and found an association between standing (IMS ≥ 4) and a reduced risk of ICUAW [281]. Similarly, Shimogai et al. also showed in their retrospective analysis of 155 ICU patients that regardless of disease severity, age and functional status prior to hospital admission,

IMS ≥ 4 (standing) within five days of ICU admission increased the likelihood of being discharged home [282].

The paper published by Scheffenbichler et al. on the influence of mobilisation dose demonstrated an independent effect of a higher mobilisation level on adverse discharge [258].

(Early) mobilisation should be performed at the highest possible level according to the current state of research, whereby, in particular, the standing (IMS ≥ 4) appears to be an important milestone in improving treatment outcomes.

Recommendation 3.16 (new 2022)
We recommend mobilising to the highest possible mobilisation level. Optimally, the patient should stand, actively transfer from bed to chair, or walk (SOMS ≥ 3 or IMS ≥ 4).
Grade of recommendation: strong
Level of evidence: 3
Consensus strength:
Literature: LoE 3: Scheffenbichler *et al.* [259]; Raurell-Torredà *et al.* [281]

5.10 Clinical question: How should mobilisation be implemented into intensive care?

The therapy of ICU patients includes many different aspects, such as ventilation or weaning from ventilation, treatment of delirium, pain and sedation as well as family. In clinical practice, it can be challenging to coordinate all these aspects.

In a prospective cohort study, Hsieh et al. first introduced a protocol for awakening trials and monitoring and managing delirium in two ICUs. In the second step, a protocol for mobilisation and coordination of the different bundle elements was established in one of the ICUs. Daily spontaneous breathing trials were already standard practice in both ICUs before the start of the study. They were able to show that only the introduction of the complete bundle, consisting of awakening trials, spontaneous breathing trials, delirium monitoring and management, (early) mobilisation as well as coordination of the different elements, led to an improvement in the treatment outcome measured by the duration of ventilation, length of stay in the ICU and the hospital [283].

The network meta-analysis by Matsuura et al. examined non-pharmacological interventions with several components for delirium prevention, which had a protective effect on delirium.

The combination of sleep promotion and cognitive stimulation showed the strongest effect followed by the combination of sleep promotion, cognitive stimulation, early mobilisation, pain therapy and patient assessment as second best [284].

Chen et al. conducted an identical network meta-analysis. In a similar fashion, non-pharmacological intervention consisting of multiple components (including early mobilisation) significantly reduced the incidence of delirium, whereas no effect was detected for early mobilisation alone. There is potentially a synergistic effect between the individual components [285].

5.10.1 The ABCDEF-Bundle

The ABCDEF bundle [286] consists of the components A (assessment, prevention and management of pain), B (both spontaneous awakening trial and spontaneous breathing trial), C (choice of analgesia and sedation), D (delirium: assess, prevent, and manage), E (early mobility and exercise) and F (Family engagement and empowerment) (see Figure 5) [287].

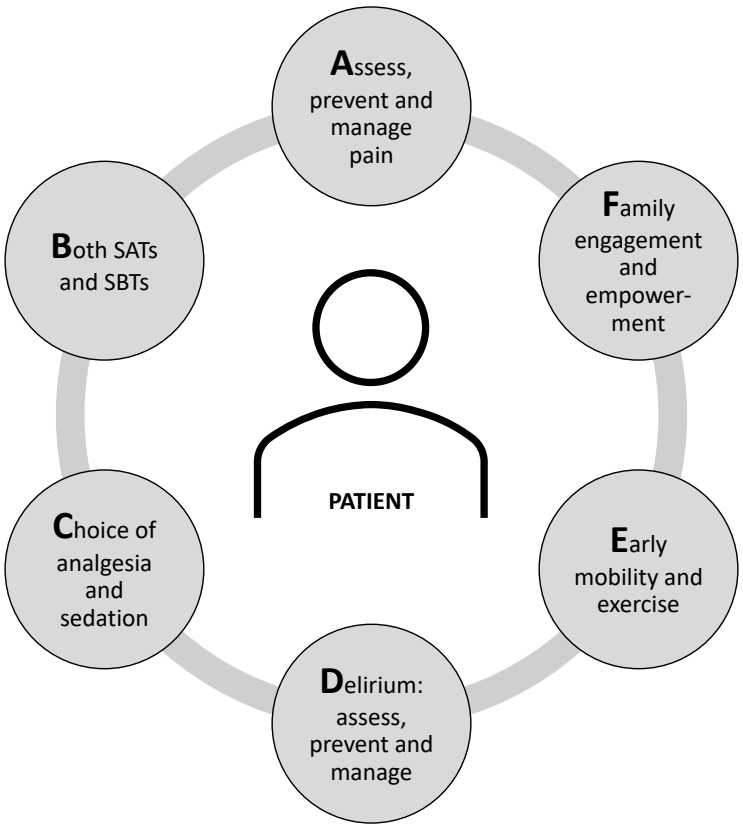

Figure 5. ABCDEF bundle adapted from Society of Critical Care Medicine [286]

In a prospective observational study by Collinsworth et al. high adherence to the ABCDE bundle increased the likelihood to be discharged home, and reduced hospital LOS and mortality. Individual effect of the bundle elements cannot be determined based on the analyses [288].

Barnes-Daly et al. reported that bundle adherence was associated with decreased in-hospital mortality and cognitive dysfunction in a prospective cohort study of over 6000 patients [289].

In a large retrospective and prospective cohort study of more than 15,000 patients, Pun et al. showed that complete adherence to the ABCEDF bundle positively affected the treatment outcome, which decreased with the degree of non-compliance. Complete bundle adherence increased the likelihood of discharge from the ICU and the hospital, reduced mortality risk and increased the likelihood of extubation on the following day. In addition to the short-term effects, adherence to the ABCDEF bundle was associated with a lower likelihood of ICU readmission and a higher likelihood of discharge home [290].

The individual bundle elements are also reflected in the intensive care quality indicators [291] published by the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI).

Table 4. Main indicators of intensive care medicine (according to DIVI; 4th edition) [291]

I	Daily multiprofessional and interdisciplinary ward rounds with documentation of daily goals
II	Management of sedation, analgesia and delirium
III	Patient-adapted ventilation (for severe lung failure)
IV	Early weaning from invasive ventilation
V	Monitoring of infection prevention measures
VI	Infection management measures
VII	Patient-adapted nutrition
VIII	Structured communication with patients and relatives
IX	Early mobilisation
X	Head of the intensive care unit

Early mobilisation has been included as one of the main indicators since 2017 providing a step-by-step approach to the structural implementation of early mobilisation in the ICU [291].

5.10.2 Evaluation and recommendation on bundle approaches

The available evidence indicates a synergistic effect of the different therapies that an ICU patient receives, leading to the recommendation of a coordinated approach based on a bundle, e.g. the ABCDEF bundle.

Recommendation 3.17 (modified 2022)
We recommend the integration of (early) mobilisation into a treatment bundle covering the management of pain, anxiety, agitation and delirium, and conduction of spontaneous breathing trials in ventilated patients (e.g., ABCDEF bundle).
Level of recommendation: strong
Level of evidence: 3
Consensus strength: guideline members 100%; professional societies 100%.
Literature: *ABCDEF-Bundle:* LoE 3: Hsieh *et al.* [283]; Pun *et al.* [290]; Barnes-Daly *et al.* [289]; Frade-Mera *et al.* [292] LoE 4: Collinsworth *et al.* [288]; Bounds *et al.* [293]; Balas *et al.* [294] LoE 5: Chen *et al.* [295] *others:* LoE 1: Chen *et al.* [285] LoE 2: Matsuura *et al.* [284] LoE 4: Martinez *et al.* [296]; Smith *et al.* [297] LoE 5: Escalon *et al.* [298]

5.11 Clinical question: How can nutrition supplement (early) mobilisation?

Muscle loss has been reported to be as high as 12.5% within the first seven days of critical illness [133]. In addition, 40% of patients develop pronounced muscle weakness, which can lead to quadriplegia [299, 300]. In healthy subjects, increased protein intake and muscle training significantly increase muscle strength and mass [301]. Therefore, protein intake was also investigated in critically ill patients with a wide variety of rehabilitation programs, which likely explains the heterogeneous results of these studies.

Ferrie et al. investigated the effect of 0.8 g/kg/d and 1.2 g/kg/d protein in a double-blinded intervention study. No difference in hand strength at ICU discharge was found. Also, the favourable effect on nitrogen balance on day 3 was no longer there on day 7. However, there was a positive effect on muscle cross-sectional area in ultrasound. Length of stay, duration of ventilation and mortality remained unaffected [302].

In the randomised controlled pilot study by Fetterplace et al., protein supplementation increased protein intake while reducing the loss of muscle cross-section at discharge from the ICU. However, there was no effect on muscle strength or physical function [303].

In a meta-analysis by Lee et al., 19 studies comparing high and low protein intake were examined. There was no effect on mortality, duration of ventilation, hospital or ICU LOS. However, high protein intake reduced muscle atrophy during the ICU stay [304].

In contrast to exercise in healthy individuals, there is evidence from an observational study of 66 ventilated patients that intensive early mobilisation was associated with only a slight increase in calorie consumption (20 minutes of mobilisation with active transfer to a chair and back required less than five additional calories) [305].

The interaction of diet and exercise in critically ill patients is complex, and results from initial studies are contradictory. Nakamura et al. showed that increased protein intake combined with mobilisation and electrical muscle stimulation led to a significant decrease in muscle atrophy. The effect was absent when the patients did not receive electrical muscle stimulation [306]. In the RCT by de Azevedo et al., combining a high protein intake with daily supine cycling led to significantly improved physical quality of life three and six months after discharge. In addition, the intervention group had more handgrip strength and reduced mortality compared with the control group [307]. The pilot study by Kagan et al. also investigated the combination of supine cycling and high protein intake, which showed no effect on ICU LOS, hospital LOS or duration of ventilation. In contrast to the results by Azevedo et al., there was no effect on mortality. Physical function or muscle strength were not studied [307, 308].

First monocentric studies show promising results regarding the combination of increased protein intake and (early) mobilisation. However, the number of studies is insufficient to make a recommendation currently, and further scientific studies of the question are necessary. Further multi-centre studies (e.g., NEXIS trial) are currently conducted [309]).

Recommendation 3.18 (new 2022)
We are unable to make a recommendation for or against the combination of mobilisation with increased protein intake.
Grade of recommendation: [-]
Evidence level: 5 (expert consensus)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Nakamura *et al.* [306]; de Azevedo *et al.* [307] LoE 4: Kou *et al.* [310], Nakano *et al.* [311] LoE 5: Wappel *et al.* [312] No effect: LoE 2: Kagan *et al.* [308]

5.12 Clinical question: How should relatives be involved in the (early) mobilisation of critically ill patients?

Critical illness and the associated therapy in the intensive care unit is a significant burden for patients. In recent years, it has been shown that not only the patients but also their relatives suffer from the situation [313]. In addition to investigating the patients' distress associated with the ICU stay, the burden on relatives has also come into scientific focus. One approach to alleviate this burden is involvement in care. For example, the ABCDE bundle has now been extended to ABCDEF (F for family) to consider this.

In their systematic review, van Delft et al. investigated the acceptance of involving relatives in care and the effects of this very involvement. The attitude towards involving relatives in care was positive for the treatment team, the patients, and their relatives. As there are few studies with relatives involved in mobilisation, no statement on its actual effect was possible [314].

Due to the limited evidence, it is not possible at this stage to recommend caregivers' involvement in mobilisation. However, the positive attitude of all stakeholders towards involvement shows that further studies in this area are necessary.

Recommendation 3.19 (new 2022)
We are unable to make a recommendation for or against the involvement of relatives in (early) mobilisation.
Grade of recommendation: [-]
Evidence level: 5 (expert consensus)
Consensus strength: guideline members 94%; professional societies 91%.
Literature: LoE 5: van Delft *et al.* [314]

5.13 Recommendations of other guidelines

Notably, several guidelines on early mobilisation have been published and referenced in the respective chapters [126, 141, 242, 243, 248, 269, 315, 316]. Generally, early mobilisation of critically ill patients is recommended, considering differently defined safety and discontinuation criteria as well as contraindications [141, 242, 248]. ICU patients who should receive (early) mobilisation are defined based on varying criteria [141] or absence of contraindications [242]. In the present guideline, the available evidence was specifically elaborated for specific groups, such as patients undergoing ECMO or renal replacement therapy, to include these patients in (early) mobilisation under precise evaluation.

In accordance with this guideline, three of the seven published guidelines recommend daily mobilisation [242, 248, 315]. Additional emphasis was put on protocol-based (early) mobilisation [316], a structured interdisciplinary team [141, 242, 243, 269, 315] and the involvement of relatives [141, 269, 315], which are consistent with the current evidence presented in this guideline.

6 Assist devices and robotics

6.1 Definition

This chapter discusses the use of assist devices in the context of mobilisation in the ICU and compares their use with (early) mobilisation or standard of care. Assist devices include equipment-assisted measures (e.g., supine cycling, treadmill) and the use of robotics. Their use is not uniform, and they are often part of heterogeneous, multimodal study interventions in combination with (early) mobilisation, the respective standard of care or neuromuscular electrical stimulation.

Supine cycling can be used with patients lying in bed and allows motor-assisted passive, assisted-active or active cycling adapted to the patient's physical strength for the variables support/resistance and speed. Patients are supine with individually adjusted head height (e.g., semirecumbent) to allow optimal leg movement. The aim of using assistive devices is to prevent muscle deterioration through passive, active-assisted or active mobilisation and improve treatment outcomes for critically ill patients. The use and adjustment of assistive devices must also be trained, respecting the respective manufacturer's instructions.

6.2 6.2 Effects and Impacts

The interpretation of the available studies on the effect of supine cycling on patient-oriented treatment outcomes is almost impossible due to the heterogeneous study protocols concerning the intervention and control groups and the definition of treatment outcomes. The assist devices were evaluated in combination with early mobilisation, with mobilisation, and as part of multimodal rehabilitation concepts. Likewise, the control groups were standard of care or (early) mobilisation. The endpoints ranged from functionality and muscle strength to duration of ventilation and ICU and hospital LOS.

6.2.1 Clinical question: Is adding supine cycling with early mobilisation beneficial?

Based on the available evidence, the combination of bed cycling with (early) mobilisation did not show any improvement in functionality (Barthel Index, MRC, 6MWD, Katz Index of Independence, FIM) or quality of life (SF-36) [279, 317, 318]. Similarly, no effect could be

demonstrated on the muscular level: respiratory muscle strength, lower limb muscle resistance and rectus femoris thickness were not significantly improved in the early mobilisation and bed cycling groups compared to early mobilisation alone [318].

Duration of ventilation was not affected by the additional use of supine cycling compared to the control group in eight of nine RCTs and meta-analyses [164, 177, 317, 319-324]. Similarly, bed cycling did not reduce ICU and hospital LOS in seven of nine RCTs and meta-analyses [164, 177, 317, 319-323, 325].

Recommendation 4.1 (modified 2022)
We are unable to make a recommendation for or against the use of supine cycling in combination with (early) mobilisation.
Grade of recommendation: [-]
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Waldauf *et al.* [317]; Eggmann *et al.* [279]; Fossat *et al.* [318] LoE 3: Nickels *et al.* [326]

6.2.2 Clinical question: Can supine cycling be considered in the context of mobilisation?

Recommendation 4.2 (modified 2022)
We suggest considering supine cycling in the context of early mobilisation if functional training is not sufficiently possible.
Grade of recommendation: weak
Level of evidence: 1
Consensus strength: guideline members 94%; professional societies 91%.
Literature: LoE 1: Waldauf *et al.* [164] LoE 2: Waldauf *et al.* [317]; Fossat *et al.* [318]; Eggmann *et al.* [279]; Ribeiro *et al.* [177]; Takaoka *et al.* [319]; Berney *et al.* [327]; Nickels *et al.* [326]; Medrinal *et al.* [328]; Dos Santos Machado *et al.* [321]; Bianchi *et al.* [323]; Kwakman *et al.* [329]; Burtin *et al.* [322]; Gama Lordello *et al.* [330]; Windmöller *et al.* [331]

6.3 Safety aspects, side effects and contraindications

6.3.1 Clinical question: Is supine cycling safe, or are there patients for whom supine cycling is contraindicated?

Supine cycling is considered safe when contraindications are considered [279, 319, 320, 328]. Complications are rare and not statistically significant compared to the control group not performing in-bed cycling. Only one RCT by Waldauf et al. showed increased intracranial pressure elevations in the intervention group who received a progressive mobility programme with 90 minutes of daily active exercise, including functional electrical stimulation and bed cycling. In the subgroup of patients with intracranial pressure monitoring, the combination of early mobilisation, NMES and supine cycling led to an increase in intracranial pressure compared to early mobilisation alone [317].

In patients after elective cardiac surgery, integrating supine cycling into rehabilitation reduced the length of stay; however, it should be noted that the patient cohort consisted of postoperative patients without any organ dysfunction [177]. For patients with acute respiratory failure, using supine cycling led to improved functionality, reduced duration of mechanical ventilation and shortened ICU length of stay [320].

Recommendation 4.3 (new 2022)
We recommend monitoring intracranial pressure in patients at risk of intracranial pressure elevations when using a bedside bicycle.
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 94%; professional societies 91%.
Literature: LoE 2: Waldauf *et al.* [317]

6.4 Clinical question: Which setting for supine cycling should be used?

In-bed cycling can be used for passive (pre-set cadence) and active exercise (with or without resistance). Cardiorespiratory status, level of alertness or sedation, willingness to cooperate and global muscle strength must be assessed by the intensive care team based on which the mode can be set accordingly. However, functional training should be prioritised over even the highest possible training intensity of supine cycling [279, 318, 320].

There is little difference between early mobilisations with and without supine cycling. Early start of mobilisation therapy, as well as active training, should be focused on.

The cadence for passive bed cycling for unresponsive patients in study protocols is usually 20 per minute for 20-30 minutes. Patients must be closely monitored for active modes to not exceed individual heart rate limits. Verbal or device prompts may increase active participation in sedated patients. To avoid overexertion, another cycle can be performed after recovery to baseline values. Sessions may be terminated early at the patient's request or if there are safety concerns [279, 318, 322, 326, 332].

6.5 Robotics

6.5.1 Definition

Robotics is not a therapy concept on its own but a way of overcoming barriers to (early) mobilisation, such as a lack of staff. [333-335]. Therefore, appropriate endpoints for using robotics are a higher probability of (early) mobilisation or staff retention in the context of (early) mobilisation. Robotics-assisted measures for (early) mobilisation include automated systems that can perform mobilisations independently of staff or respond to patients in a self-adaptive way [334].

6.5.2 Clinical question: Does using robotics in addition to (early) mobilisation have a positive effect?

Suitable studies investigating the benefit of robotics in the context of (early) mobilisation currently do not exist. Therefore, no recommendation for or against using robotics can be made. From the expert panel’s point of view, a possible benefit under local conditions should be evaluated before purchasing any robotic systems.

6.5.3 Clinical question: Is the use of treadmills with body weight support beneficial?

We cannot recommend for or against using treadmills with body weight support but emphasise the need for studies in that field [334, 335].

Recommendation 4.4 (new 2022)
We cannot currently make a recommendation for or against the use of assist devices (e.g., tilt tables, treadmills with body weight support) or robotic systems.
Grade of recommendation: [-]
Evidence level: 5 (expert consensus)
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 2: Kwakman *et al.* [329] LoE 3: Frazzitta *et al.* [336] LoE 4: Sommers *et al.* [337]

7 Neuromuscular electrical stimulation (NMES)

7.1 Definition and rationale

NMES describes a non-invasive, therapeutic intervention in which transcutaneous application of electrical stimuli leads to an active muscle contraction independently of the patient's cooperation. This can be of interest, especially in the early phase of critical illness, when patients are often unable to make an active contribution to early mobilisation due to sedation. Importantly, the early phase of critical illness is a vulnerable phase during which pathophysiological processes can be highly relevant for treatment outcomes. This is also reflected in the fact that an early start of mobilisation leads to more pronounced beneficial effects than a later start.

In addition to the early start, a longer duration and a higher level of mobilisation are associated with an improved treatment outcome [258, 259], reflected in the recommendations of this guideline. Therefore, NMES can be an important tool for implementing these two recommendations in non-cooperative patients due to the characteristics previously described as facilitating early and active mobilisation.

7.2 Clinical question: Should neuromuscular electrical stimulation be performed in the context of early mobilisation of intensive care patients?

In a monocentric RCT from 2018, Fossat et al. investigated the effect of 15 minutes of bed cycling and sequential 50 minutes of NMES of the quadriceps femoris muscles in addition to usual care on muscle strength. In 314 randomised patients, muscle strength (MRC score at ICU discharge - median [interquartile range]: intervention 48 [29-58] vs control 51 [37-58]; p = 0.28) and secondary outcomes (mobility level, delirium, duration of ventilation, mortality, muscle mass, activities of daily living, follow-up at six months) were not different between the intervention and control group. No serious adverse events occurred during the study, and the overall number of clinically significant adverse events was very low (intervention: 7/4159 (0.2%), control: 12/1190 (1.0%) mobilisations). NMES was the safest intervention compared to regular rehabilitation and bed cycling [318].

In the randomised controlled trial by Gerovasili et al. from 2009, 49 patients stratified by age and sex were included. Patients in the intervention group received 55 minutes of NMES of the quadriceps femoris and peronei longi muscles daily between the second and ninth day after ICU admission. Consecutive ultrasound scans on the day of randomisation and after seven or eight days showed that muscle mass loss was significantly reduced in the intervention group compared to the control group [338].

In their systematic review from 2021, Gutiérrez-Arias et al. investigated whether NMES affected the duration of ventilation in ICU patients. Twelve randomised controlled trials that investigated NMES in ventilated patients were included. A meta-analysis from ten studies showed a significant reduction in ventilation time (mean difference (95%CI): -2.68 days (4.35 - 1.02); p = 0.02). Furthermore, only three studies showed adverse events [339].

Liu et al. investigated the effect of NMES on the development of ICUAW in their systematic review. Eleven studies were included in the systematic review, whereas depending on the endpoints, only between two and six studies could be considered for meta-analysis. A beneficial effect of NMES was shown for the endpoints muscle strength, duration of ventilation, hospital and ICU LOS, and physical function. In contrast, mortality risk was unaffected [340].

Zayed et al. addressed the same study question. They could not demonstrate any effect of NMES on muscle strength, ICU LOS, mortality, and duration of ventilation in a meta-analysis of five studies [341].

Waldauf et al. conducted a meta-analysis on ICU rehabilitation and independently evaluated the effects of NMES. In an analysis of 14 studies, NMES did not affect LOS or mortality, but there was a reduction in the duration of ventilation [164].

A similar approach was taken by Anekwe et al., who considered a total of nine studies for the systematic review, of which only three studies performed NMES and one study performed (early) mobilisation with NMES. Analysis of the four studies revealed that NMES reduced the risk of ICUAW. In a subgroup analysis, however, this effect was only present in the studies that exclusively investigated NMES [163].

The International Classification of Functioning, Disability and Health (ICF) measures health and potential limitations. In their systematic review, Burke et al. looked at the effect of NMES on the ICF. Of the twelve included studies, three could be considered for the meta-analysis. The meta-analysis showed a significantly improved muscle strength for the intervention NMES [342]. The same result was found in the meta-analysis by Wageck et al., which included nine studies and considered two of them for the quantitative analysis of muscle strength [343].

In many meta-analyses, beneficial effects of NMES on treatment outcomes are demonstrated. The heterogeneity of these effects is likely explained by the different inclusion criteria of the systematic reviews, the heterogeneous selection of endpoints within the primary literature and the search periods. Furthermore, the quality of the meta-analyses is limited due to the frequently high drop-out rates for the analyses. There needs to be more high-quality randomised controlled trials with enough cases to evaluate relevant patient-centred endpoints. Nevertheless, due to the safety of the intervention and its positive effects, NMES can be considered in the context of (early) mobilisation [339, 344].

Regarding the NMES protocols, no recommendation can be made as there are no systematic studies at this time. Available studies used different stimulation parameters and found no harmful effects (Table 5) except for one study with exceptionally high currents, which led to skin burns [345]. Accordingly, this harmful setting was not included in the compilation of parameters below (Table 5). Of note, based on a study by Grunow et al., muscle contraction seems necessary to achieve clinical benefit. Based on their findings, a stimulation with 50.1 mA can identify patients for whom NMES is beneficial with a sensitivity of 100% and specificity of 84.6% [346].

Table 5: Safety criteria for starting mobilisation from previous publications [324, 345, 347-349]

Parameter	lowest values	highest values
Duration (min)	20	110
Intensity (mA)	2	140
Frequency (Hz)	20	100

Recommendation 5.1 (new 2022)
We suggest to consider neuromuscular electrical stimulation in the context of early mobilisation of intensive care patients.
Grade of recommendation: weak
Level of evidence: 2
Consensus strength: guideline members 100%; professional societies 100%.
Literature: LoE 1: Gutiérrez-Arias *et al.* [339]; Liu *et al.* [340] LoE 2: Nakanishi *et al.* [350]; Waldauf *et al.* [164]; Anekwe *et al.* [163]; Zayed *et al.* [341]; Fossat *et al.* [318]; Burke *et al.* [342]; Wageck *et al.* [343]; Gerovasili *et al.* [338]; Routsi *et al.* [351]

7.3 Clinical question: Is neuromuscular electrical stimulation safe in intensive care patients?

NMES is generally a safe intervention [339, 344]. In the monocentric RCT by Waldauf et al., the intervention protocol-based physiotherapy with functional electrical stimulation (combination of NMES and in-bed cycling) was compared to standard of care. Intracranial pressure (ICP) was monitored in four patients in the intervention group and three in the control group. Notably, there were 23 episodes of increased ICP in the intervention group during a cumulative 15 days of ICP monitoring, i.e., 1.5 episodes per day of ICP monitoring and no ICP increase in the control group. In contrast, the ICP increases did not occur during or immediately after the study intervention. In addition, the intervention group showed poorer health-related quality of life in the cognitive domain [317].

Based on the subgroup analysis with significantly more episodes of elevated ICP, it is recommended that patients at risk of elevated ICP should be continuously monitored.

Recommendation 5.2 (new 2022)
We recommend monitoring intracranial pressure in patients at risk of intracranial pressure elevations when using neuromuscular electrical stimulation (NMES).
Grade of recommendation: strong
Level of evidence: 2
Consensus strength: guideline members 94%; professional societies 91%.
Literature: LoE 2: Waldauf *et al.* [317]

8 Important research questions

Many questions covered by this guideline still need to be studied more, so we focus on the most important ones of each chapter.

In the area of positioning, there are no studies on the effect of seated in-bed positioning (elevated upper body and legs bent and lying downwards) and few on the positioning of awake patients. Furthermore, the effects of increased PEEP or prone positioning on intra-abdominal pressure are inconsistent and require further research. In the case of prone positioning, the following essential questions are inadequately addressed: (1) is prone positioning for more than 16 hours of clinical benefit, (2) what is the optimal PEEP during prone positioning, and (3) when should prone positioning therapy be stopped raising the question of how to identify success or failure of prone positioning. Similarly relevant for clinical practice is the question of whether the use of positioning aids to perform prone positioning improves the beneficial effects of prone positioning therapy described above - homogenisation of lung ventilation and improvement of the ventilation-perfusion ratio - or reduces adverse effects such as skin damage (intertrigo or pressure sores).

In the area of (early) mobilisation, the most crucial point to be clarified is the adequate dose of mobilisation, as the results of the TEAM RCT confirmed [273, 280]. How optimal (early) mobilisation can be performed to lead to the best possible treatment outcome should be urgently investigated in previously functionally dependent and functionally independent patients. It is also necessary to clarify whether and how neuro-ICU patients can benefit most. Especially after aneurysmal subarachnoid haemorrhage with the risk of vasospasm, randomised controlled trials are needed. Further identification of patient cohorts and their benefit from mobilisation may enable the development of an individualised approach in the future, particularly by Big Data and Machine Learning [352]. For clinical practice, an expansion of the evidence for start and stop criteria of (early) mobilisation would be needed.

Due to the lack of ICU staff, robotics and assist devices are exciting topics that deserve attention. In addition to relieving staff, such systems have the potential to enable individually adapted mobilisation via (bio-)feedback systems. Of note, these developments tailored to ICU patients have only started. Compared to other medical fields, ICU patients cannot support the robotic systems during acute illness. Therefore, fully automated systems (or with only

extremely low/short-term effort) are necessary for the attachment and set-up to relieve the ICU staff. It must also be possible to carry out mobilisation safely without staff involvement.

Currently, neuromuscular electrical stimulation often only stimulates the lower extremity/quadriceps femoris. Modern systems of the future may achieve a better training effect by stimulating several muscle groups with little preparation effort, individualised training programmes, and relieving staff.

9 Composition of the guideline group in detail

9.1 Participating professional societies and organisations

Table 6. Members of the Guideline Group

Mandate holder	Professional society/ organisation	Period
Bein, Thomas	DGAI	from 03.11.2020
Bingold, Tobias	DGAI	03.11.2020 bis 10.02.2022
Blobner, Manfred	DGAI	from 03.11.2020
Brückner, Uta	ZVK	03.11.2020 to 23.06.2022
Coldewey, Sina M.	DGAI	from 03.11.2020
Grunow, Julius	DGAI	from 03.11.2020
Hamsen, Uwe	DGCH	from 17.08.2021
Hermes, Carsten	DGIIN	from 03.11.2020
Jung, Sven	DGCH	25.06.2021 to 17.08.2021
Kaltwasser, Arnold	DIVI	from 03.11.2020
Kredler, Dennis	Patient representatives (Global Sepsis Alliance)	from 03.11.2020
Lewald, Heidrun	DGAI	from 03.11.2020
Nydahl, Peter	DGNI	from 03.11.2020
Reißhauer, Anett	DGPRM	from 03.11.2020
Renzewitz, Leonie	ZVK	from 23.06.2022
Schaller, Stefan J.	DGAI	from 03.11.2020
Scheffenbichler, Flora	DGAI	from 03.11.2020
Simon, Karsten	DGP	from 03.11.2020
Staudinger, Thomas	ÖGIAIN	from 03.11.2020
Ullrich, Roman	ÖGARI	from 03.11.2020
Weber-Carstens, Steffen	DGAI	from 03.11.2020
Wrigge, Hermann	DGAI	from 03.11.2020
Zergiebel, Dominik	DGF	from 03.11.2020

9.2 Patient/citizen participation

The guideline was prepared with the direct participation of the patient representative Dennis Kredler who was entitled to vote and was involved in the preparation and writing of the guideline.

9.3 Methodical accompaniment

Monika Nothacker, MD, AWMF Guideline Advisor, provided methodological support in the preparation/updating of the guideline.

10 Information on this guideline

10.1 Methods

The methods used to prepare this guideline are based on the AWMF regulations (version 1.1 from 02/27/2013) [353].

10.2 Systematic search and selection of evidence

A systematic literature search was performed on May 31, 2021, for articles published between January 1, 2014 and May 31, 2021. An updated search covering the time from January 1, 2021, to July 6, 2022, was performed on July 6, 2022.

A detailed description of the literature search can be found in the guideline report. The basis for the guideline update is the existing S2e guideline: "Positioning therapy and early mobilisation for the prophylaxis or therapy of pulmonary dysfunction" and the systematic literature search from 2014 to July 2022.

10.3 Critical evaluation of the evidence

The full texts included were processed using an evidence table from the Association of the Scientific Medical Societies (AWMF) [354]. The level of evidence was determined for each study using the Oxford Centre of Evidence-Based Medicine Level of Evidence document (2011 version) [355]. In the updated search, the evidence assessment system was not changed. A detailed description of the structured evidence assessment can be found in the guideline report.

10.4 Structured consensus building

Structured consensus was reached using the Delphi technique via online voting. A total of three Delphi rounds took place. Recommendations with 100% agreement were not put to the vote unless explicitly requested in the final consensus meeting. In the final hybrid structured consensus meeting moderated by the AWMF (MN), recommendations were discussed and voted on, which had not achieved a 100% agreement in the Delphi rounds before. A detailed description of the structured consensus meeting can be found in the guideline report.

10.5 Recommendation grading and determination of consensus strength

10.5.1 Determining the level of recommendation

Recommendations were graded according to GRADE (Table 7) [356].

In addition to available evidence, clinical experience was considered in the grading of the recommendations. In addition, further criteria such as consistency of the study results; clinical relevance of the endpoints and effect sizes; benefit-harm ratio; ethical, legal, and economic obligations; patient preferences; applicability to the patient target group and the German healthcare system, as well as feasibility in everyday life/different health care settings, were considered.

Table 7. Levels of recommendation according to GRADE

Recommendation level	Description	Expression
1	Strong recommendation	We recommend/ do not recommend
2	Recommendation	We suggest/do not suggest

10.5.2 Determining the strength of consensus

Only recommendations with an agreement of more than 75% (of both the professional societies represented and the nominated representatives) were included in the guideline; a strong agreement was defined as > 95%.

11 Editorial independence

11.1 Funding of the Guideline

Partial funding of a student assistant to support the guideline was provided by the German Society for Anaesthesiology and Intensive Care Medicine (DGAI).

11.2 Declaration of interests and handling of conflicts of interest

A working group without conflicts of interest (TB, SC, FS) created the criteria and defined implementation in the guideline creation. Low conflict of interest was defined as paid lecturing/training activities/authorships ≤ 1000 €/year and research projects with management responsibility with governmental funding. Moderate conflicts of interest were industry-paid lecturing/training activities or paid authorships of 1001-3000 €/year; direct commercial interests from consulting, expert, or board activities; activity in a company advisory board (distribution of products related to the guideline); company share ownership; or research projects with management responsibility funded by industry. High conflicts of interest were company-paid lecturing/training activities or paid authorship > 3000 €/year; direct commercial interests from consultant/expert/company advisory board, board of directors' activities > 3000 €/year; industry employee; owner of patents or copyrights; company share ownership > 5000 €. Members with low conflicts of interest could not take on a leading function within topic-specific expert groups, except if that position was shared. Moderate conflicts of interest did not allow voting, while they could participate in the discussion. For panel members with high conflicts of interest, commenting was also not permitted; they could only hand in a written statement on that topic. Conflicts of interest were categorised into subject areas for which the restrictions applied. Each panel member submitted Conflicts of interest yearly based on the AWMF's "Declaration of interests and handling of conflicts of interest in guideline projects" [357] which are publicly accessible on the website of AWMF.

The heterogeneous composition of the guideline panel, application of the Delphi process, external moderation, transparency of conflicts of interest and their consequences, as well as

a public consultation phase of the guideline, could reduce a possible bias caused by conflicts of interest. Details on conflict-of-interest regulations can be found in the guideline report.

11.3 External evaluation and adoption

The long version of the guideline with all recommendations, evidence tables and the guideline report were submitted to all participating professional societies for review, comment and approval by the Presidium or Executive Committee, where they were approved accordingly.

12 Period of validity and updating procedure

The last revision of the guideline took place on 27.06.2023 by incorporating the comments of the professional societies. The guideline is valid until 31.01.2026.

The update process includes a review and assessment of the core statements based on the most recent available evidence using a systematic literature search by the editorial group and a revision of all evidence according to GRADE (currently Oxford 2011). The revised key messages will be published as part of the planned update process.

13 Abbreviations

6MWD	6-minute walk test
ABCDEF	Assessment, prevention and management of pain, Both SAT and SBT, Choice of analgesia and sedation, Delirium: assess, prevent, and manage, Early mobility an exercise, Family engagement and empowerment
ARDS	Acute Respiratory Distress Syndrome
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
BMBF	Bundesministerium für Bildung und Forschung (German Federal Ministry of Education and Research
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CPP	Cerebral Perfusion Pressure
CRRT	Continuous Renal Replacement Therapy
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
e.V.	eingetragener Verein
ECLS	Extracorporeal Life Support
EQ-5D-5L	European Quality of Life – 5 Dimensions – 5 Level
ESICM	European Society of Intensive Care Medicine
FIM	Functional Independence Measure
F_iO_2	inspiratorische Sauerstoffkonzentration
GCS	Glasgow Coma Scale
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IAP	Intraabdominal Pressure

ICF	International Classification of Functioning, Disability and Health
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit Acquired Weakness
IMS	ICU Mobility Scale
IQR	Interquartile Range
CLRT	Continuous lateral rotation therapy
LoE	Level of Evidence
MAP	Mean Arterial Pressure
MD	Mean Difference
MRC	Medical Research Council
NMES	Neuromuscular electrical stimulation
OR	Odds Ratio
P/F-Ratio	Ratio of arterial oxygen partial pressure to fractional inspired oxygen
PADIS	Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption
PaO_2	Arterial oxygen partial pressure
PBW	Predicted Body Weight
PEEP	Positive Endexpiratory Pressure
PICO	Patient/Population, Intervention, Comparison, Outcome
PICS	Post Intensive Care Syndrom
RCT	Randomized Controlled Study
RD	Risk Difference
RR	Risk Ratio
SAT	Spontaneous Awakening Trials

SBT	Spontaneous Breathing Trials
SD	Standard Deviation
SCCM	Society of Critical Care Medicine
SF-36	Short Form-36
SOFA-Score	Sequential Organ Failure Assessment-Score
SOMS	Surgical ICU Optimal Mobilisation Score
SpO_2	Oxygen saturation
VAP	Ventilator Associated Pneumonia
vv-ECMO	Veno venous - Extracorporeal Membrane Oxygenation

14 References

1. ÄZQ. (2006) Handbuch zur Entwicklung regionaler Leitlinien. *https://www.aezq.de/mdb/edocs/pdf/schriftenreihe/schriftenreihe26.pdf*, accessed on 19.01.2023
2. Dillon A, Munro CL, Grap MJ, (2002) Nurses' accuracy in estimating backrest elevation. Am J Crit Care 11: 34-37. *https://doi.org/10.4037/ajcc2002.11.1.34*
3. Zhuo X, Pan L, Zeng X, (2021) The effects of the 45 degrees semi-recumbent position on the clinical outcomes of mechanically ventilated patients: a systematic review and meta-analysis study. Ann Palliat Med 10: 10643-10651. *https://doi.org/10.21037/apm-21-2359*
4. Gocze I, Strenge F, Zeman F, Creutzenberg M, Graf BM, Schlitt HJ, Bein T, (2013) The effects of the semirecumbent position on hemodynamic status in patients on invasive mechanical ventilation: prospective randomized multivariable analysis. Crit Care 17: R80. *https://doi.org/10.1186/cc12694*
5. Huttner H. (2023) Intrakranieller Druck (ICP), S1-Leitlinie. *https://register.awmf.org/de/leitlinien/detail/030-105*, accessed on 12.05.2024
6. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment S, (2013) Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 39: 1190-1206. *https://doi.org/10.1007/s00134-013-2906-z*
7. Wang L, Li X, Yang Z, Tang X, Yuan Q, Deng L, Sun X, (2016) Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. Cochrane Database Syst Rev: CD009946. *https://doi.org/10.1002/14651858.CD009946.pub2*
8. Pozuelo-Carrascosa DP, Cobo-Cuenca AI, Carmona-Torres JM, Laredo-Aguilera JA, Santacruz-Salas E, Fernandez-Rodriguez R, (2022) Body position for preventing ventilator-associated pneumonia for critically ill patients: a systematic review and network meta-analysis. J Intensive Care 10: 9. *https://doi.org/10.1186/s40560-022-00600-z*
9. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME, (2009) Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. J Crit Care 24: 515-522. *https://doi.org/10.1016/j.jcrc.2008.09.003*
10. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer N, (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 354: 1851-1858. *https://doi.org/10.1016/S0140-6736(98)12251-1*
11. Safdar N, Dezfulian C, Collard HR, Saint S, (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 33: 2184-2193. *https://doi.org/10.1097/01.ccm.0000181731.53912.d9*
12. Warren DK, Shukla SJ, Olsen MA, Kollef MH, Hollenbeak CS, Cox MJ, Cohen MM, Fraser VJ, (2003) Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Crit Care Med 31: 1312-1317. *https://doi.org/10.1097/01.Ccm.0000063087.93157.06*
13. Guner CK, Kutluturkan S, (2022) Role of head-of-bed elevation in preventing ventilator-associated pneumonia bed elevation and pneumonia. Nurs Crit Care 27: 635-645. *https://doi.org/10.1111/nicc.12633*

14. Burnol L, Payen JF, Francony G, Skaare K, Manet R, Morel J, Bosson JL, Gergele L, (2021) Impact of Head-of-Bed Posture on Brain Oxygenation in Patients with Acute Brain Injury: A Prospective Cohort Study. Neurocrit Care 35: 662-668. *https://doi.org/10.1007/s12028-021-01240-1*
15. Vasquez DG, Berg-Copas GM, Wetta-Hall R, (2007) Influence of semi-recumbent position on intra-abdominal pressure as measured by bladder pressure. J Surg Res 139: 280-285. *https://doi.org/10.1016/j.jss.2006.10.023*
16. McBeth PB, Zygun DA, Widder S, Cheatham M, Zengerink I, Glowa J, Kirkpatrick AW, (2007) Effect of patient positioning on intra-abdominal pressure monitoring. Am J Surg 193: 644-647; discussion 647. *https://doi.org/10.1016/j.amjsurg.2007.01.013*
17. De Keulenaer BL, De Waele JJ, Powell B, Malbrain ML, (2009) What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? Intensive Care Med 35: 969-976. *https://doi.org/10.1007/s00134-009-1445-0*
18. Cheatham ML, De Waele JJ, De Laet I, De Keulenaer B, Widder S, Kirkpatrick AW, Cresswell AB, Malbrain M, Bodnar Z, Mejia-Mantilla JH, Reis R, Parr M, Schulze R, Puig S, World Society of the Abdominal Compartment Syndrome Clinical Trials Working G, (2009) The impact of body position on intra-abdominal pressure measurement: a multicenter analysis. Crit Care Med 37: 2187-2190. *https://doi.org/10.1097/CCM.0b013e3181a021fa*
19. Samimian S, Ashrafi S, Khaleghdoost Mohammadi T, Yeganeh MR, Ashraf A, Hakimi H, Dehghani M, (2021) The Correlation between Head of Bed Angle and Intra-Abdominal Pressure of Intubated Patients; a Pre-Post Clinical Trial. Arch Acad Emerg Med 9: e23.
20. Yi M, Leng Y, Bai Y, Yao G, Zhu X, (2012) The evaluation of the effect of body positioning on intra-abdominal pressure measurement and the effect of intra-abdominal pressure at different body positioning on organ function and prognosis in critically ill patients. J Crit Care 27: 222 e221-226. *https://doi.org/10.1016/j.jcrc.2011.08.010*
21. Hough A, (1984) The effect of posture on lung function. Physiotherapy 70: 101-104.
22. Badia JR, Sala E, Rodriguez-Roisin R, (1998) Positional changes and drug interventions in acute respiratory failure. Respirology 3: 103-106. *https://doi.org/10.1111/j.1440-1843.1998.tb00106.x*
23. Li Bassi G, Panigada M, Ranzani OT, Zanella A, Berra L, Cressoni M, Parrini V, Kandil H, Salati G, Selvaggi P, Amatu A, Sanz-Moncosi M, Biagioni E, Tagliaferri F, Furia M, Mercurio G, Costa A, Manca T, Lindau S, Babel J, Cavana M, Chiurazzi C, Marti JD, Consonni D, Gattinoni L, Pesenti A, Wiener-Kronish J, Bruschi C, Ballotta A, Salsi P, Livigni S, Iotti G, Fernandez J, Girardis M, Barbagallo M, Moise G, Antonelli M, Caspani ML, Vezzani A, Meybohm P, Gasparovic V, Geat E, Amato M, Niederman M, Kolobow T, Torres A, Gravity VAPN, (2017) Randomized, multicenter trial of lateral Trendelenburg versus semirecumbent body position for the prevention of ventilator-associated pneumonia. Intensive Care Med 43: 1572-1584. *https://doi.org/10.1007/s00134-017-4858-1*
24. Meyer U, Friesacher F (2015) Intensivpflege. In: Ullrich L, Stolecki D (eds) Intensivpflege und Anästhesie. Thieme, Stuttgart
25. Hewitt N, Bucknall T, Faraone NM, (2016) Lateral positioning for critically ill adult patients. Cochrane Database Syst Rev: CD007205. *https://doi.org/10.1002/14651858.CD007205.pub2*
26. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, Brady SL, Brodsky MB, Denehy L, Elliott D, Flatley C, Harabin AL, Jones C, Louis D, Meltzer W, Muldoon SR, Palmer JB, Perme C, Robinson M, Schmidt DM, Scruth E, Spill GR, Storey CP, Render M, Votto J, Harvey MA, (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40: 502-509. *https://doi.org/10.1097/CCM.0b013e318232da75*
27. Grunow JJ, Nydahl P, Schaller SJ, (2022) [Mobilization of Intensive Care Unit Patients: How Can the ICU Rooms and Modern Medical Equipment Help?]. Anasthesiol Intensivmed Notfallmed Schmerzther 57: 41-51. *https://doi.org/10.1055/a-1324-0627*

28. Nessizius S, (2017) [Customised early mobilisation : How about a little bit more?]. Med Klin Intensivmed Notfmed 112: 308-313. https://doi.org/10.1007/s00063-017-0280-2
29. Rostetter R, Jenni B, Eggmann S, Meyer JT, Schmitt KU, (2022) Implementing an interprofessional user-centered design approach to develop a bedside leg exercise device. Technol Health Care 30: 981-992. https://doi.org/10.3233/THC-213511
30. Bellgardt M, Bürkle H, Heymann A, Horter J, Kleinschmidt S, Müller A, Müller-Brandes C, Putensen C, Spies C, Schallner N, Treskatsch S, Tonner P, Trieschmann U, Wappler F, Weiß B, Deffner T, Hansen H, Hermes C, Hierundar A, Markewitz A, Sayk S, Waydhas C. (2020) S3-Leitlinie Analgesie, Sedierung und Delirmanagement in der Intensivmedizin (DAS-Leitlinie 2020). https://register.awmf.org/assets/guidelines/001-012l_S3_Analgesie-Sedierung-Delirmanagement-in-der-Intensivmedizin-DAS_2021-08.pdf, accessed on 13.05.2024
31. Staudinger T, Bojic A, Holzinger U, Meyer B, Rohwer M, Mallner F, Schellongowski P, Robak O, Laczika K, Frass M, Locker GJ, (2010) Continuous lateral rotation therapy to prevent ventilator-associated pneumonia. Crit Care Med 38: 486-490. https://doi.org/10.1097/CCM.0b013e3181bc8218
32. Schieren M, Piekarski F, Dusse F, Marcus H, Poels M, Wappler F, Defosse J, (2017) Continuous lateral rotational therapy in trauma-A systematic review and meta-analysis. J Trauma Acute Care Surg 83: 926-933. https://doi.org/10.1097/TA.0000000000001572
33. Hanneman SK, Gusick GM, Hamlin SK, Wachtel SJ, Cron SG, Jones DJ, Oldham SA, (2015) Manual vs automated lateral rotation to reduce preventable pulmonary complications in ventilator patients. Am J Crit Care 24: 24-32. https://doi.org/10.4037/ajcc2015171
34. Delaney A, Gray H, Laupland KB, Zuege DJ, (2006) Kinetic bed therapy to prevent nosocomial pneumonia in mechanically ventilated patients: a systematic review and meta-analysis. Crit Care 10: R70. https://doi.org/10.1186/cc4912
35. Schieren M, Wappler F, Klodt D, Sakka SG, Lefering R, Jacker V, Defosse J, (2020) Continuous lateral rotational therapy in thoracic trauma--A matched pair analysis. Injury 51: 51-58. https://doi.org/10.1016/j.injury.2019.11.009
36. Wutzler S, Sturm K, Lustenberger T, Wyen H, Zacharowksi K, Marzi I, Bingold T, (2017) Kinetic therapy in multiple trauma patients with severe thoracic trauma: a treatment option to reduce ventilator time and improve outcome. Eur J Trauma Emerg Surg 43: 155-161. https://doi.org/10.1007/s00068-016-0692-3
37. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y, (2007) Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 33: 66-73. https://doi.org/10.1007/s00134-006-0399-8
38. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, Khoo TM, Ali SB, Saman MA, Shaltut A, Tan CC, Yong CY, Bailey M, (2013) Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 39: 910-918. https://doi.org/10.1007/s00134-013-2830-2
39. (2018) Impact of oversedation prevention in ventilated critically ill patients: a randomized trial-the AWARE study. Ann Intensive Care 8: 93. https://doi.org/10.1186/s13613-018-0425-3
40. Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ, (2000) Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. Crit Care Med 28: 295-303. https://doi.org/10.1097/00003246-200002000-00001
41. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ, (1997) Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. Crit Care Med 25: 16-27. https://doi.org/10.1097/00003246-199701000-00007
42. Galiatsou E, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G, (2006) Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. Am J Respir Crit Care Med 174: 187-197. https://doi.org/10.1164/rccm.200506-899OC

43. Protti A, Santini A, Pennati F, Chiurazzi C, Ferrari M, Iapichino GE, Carenzo L, Dalla Corte F, Lanza E, Martinetti N, Aliverti A, Cecconi M, (2022) Lung response to prone positioning in mechanically-ventilated patients with COVID-19. Crit Care 26: 127. https://doi.org/10.1186/s13054-022-03996-0
44. Katira BH, Osada K, Engelberts D, Bastia L, Damiani LF, Li X, Chen H, Yoshida T, Amato MBP, Ferguson ND, Post M, Kavanagh BP, Brochard LJ, (2021) Positive End-Expiratory Pressure, Pleural Pressure, and Regional Compliance during Pronation: An Experimental Study. Am J Respir Crit Care Med 203: 1266-1274. https://doi.org/10.1164/rccm.202007-2957OC
45. Cornejo RA, Diaz JC, Tobar EA, Bruhn AR, Ramos CA, Gonzalez RA, Repetto CA, Romero CM, Galvez LR, Llanos O, Arellano DH, Neira WR, Diaz GA, Zamorano AJ, Pereira GL, (2013) Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 188: 440-448. https://doi.org/10.1164/rccm.201207-1279OC
46. Spinelli E, Kircher M, Stender B, Ottaviani I, Basile MC, Marongiu I, Colussi G, Grasselli G, Pesenti A, Mauri T, (2021) Unmatched ventilation and perfusion measured by electrical impedance tomography predicts the outcome of ARDS. Crit Care 25: 192. https://doi.org/10.1186/s13054-021-03615-4
47. Wang YX, Zhong M, Dong MH, Song JQ, Zheng YJ, Wu W, Tao JL, Zhu L, Zheng X, (2022) Prone positioning improves ventilation-perfusion matching assessed by electrical impedance tomography in patients with ARDS: a prospective physiological study. Crit Care 26: 154. https://doi.org/10.1186/s13054-022-04021-0
48. Albert RK, Keniston A, Baboi L, Ayzac L, Guerin C, Proseva I, (2014) Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med 189: 494-496. https://doi.org/10.1164/rccm.201311-2056LE
49. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L, Group PS, (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368: 2159-2168. https://doi.org/10.1056/NEJMoa1214103
50. Ayzac L, Girard R, Baboi L, Beuret P, Rabilloud M, Richard JC, Guerin C, (2016) Ventilator-associated pneumonia in ARDS patients: the impact of prone positioning. A secondary analysis of the PROSEVA trial. Intensive Care Med 42: 871-878. https://doi.org/10.1007/s00134-015-4167-5
51. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, Uleryk E, Mancebo J, Pesenti A, Ranieri VM, Fan E, (2017) Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc 14: S280-S288. https://doi.org/10.1513/AnnalsATS.201704-343OT
52. Cao Z, Yang Z, Liang Z, Cen Q, Zhang Z, Liang H, Liu R, Zeng L, Xie Y, Wang Y, (2020) Prone versus Supine Position Ventilation in Adult Patients with Acute Respiratory Distress Syndrome: A Meta-Analysis of Randomized Controlled Trials. Emerg Med Int 2020: 4973878. https://doi.org/10.1155/2020/4973878
53. Beitler JR, Shaefi S, Montesi SB, Devlin A, Loring SH, Talmor D, Malhotra A, (2014) Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. Intensive Care Med 40: 332-341. https://doi.org/10.1007/s00134-013-3194-3
54. Sud S, Friedrich JO, Adhikari NK, Taccone P, Mancebo J, Polli F, Latini R, Pesenti A, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L, Guerin C, (2014) Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 186: E381-390. https://doi.org/10.1503/cmaj.140081

55. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guerin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L, (2010) Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 36: 585-599. https://doi.org/10.1007/s00134-009-1748-1
56. Mora-Arteaga JA, Bernal-Ramirez OJ, Rodriguez SJ, (2015) The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. Med Intensiva 39: 359-372. https://doi.org/10.1016/j.medin.2014.11.003
57. Lee JM, Bae W, Lee YJ, Cho YJ, (2014) The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. Crit Care Med 42: 1252-1262. https://doi.org/10.1097/CCM.0000000000000122
58. Wang C, Wang X, Chi C, Guo L, Guo L, Zhao N, Wang W, Pi X, Sun B, Lian A, Shi J, Li E, (2016) Lung ventilation strategies for acute respiratory distress syndrome: a systematic review and network meta-analysis. Sci Rep 6: 22855. https://doi.org/10.1038/srep22855
59. Longobardo A, Snow TA, Tam K, Singer M, Bellingan G, Arulkumaran N, (2021) Non-specialist therapeutic strategies in acute respiratory distress syndrome. Minerva Anestesiol 87: 803-816. https://doi.org/10.23736/S0375-9393.21.15254-X
60. Kopterides P, Siempos, II, Armaganidis A, (2009) Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials. J Crit Care 24: 89-100. https://doi.org/10.1016/j.jcrc.2007.12.014
61. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, Brazzi L, Latini R, Prone-Supine Study G, (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345: 568-573. https://doi.org/10.1056/NEJMoa010043
62. Moran JL, Graham PL, (2021) Multivariate Meta-Analysis of the Mortality Effect of Prone Positioning in the Acute Respiratory Distress Syndrome. J Intensive Care Med 36: 1323-1330. https://doi.org/10.1177/08850666211014479
63. Cho YJ, Moon JY, Shin ES, Kim JH, Jung H, Park SY, Kim HC, Sim YS, Rhee CK, Lim J, Lee SJ, Lee WY, Lee HJ, Kwak SH, Kang EK, Chung KS, Choi WI, Korean Society of Critical Care M, Korean Academy of T, Respiratory Diseases Consensus G, (2016) Clinical Practice Guideline of Acute Respiratory Distress Syndrome. Tuberc Respir Dis (Seoul) 79: 214-233. https://doi.org/10.4046/trd.2016.79.4.214
64. Hashimoto S, Sanui M, Egi M, Ohshimo S, Shiotsuka J, Seo R, Tanaka R, Tanaka Y, Norisue Y, Hayashi Y, Nango E, Medicine AcpgcftJSoRC, the Japanese Society of Intensive Care M, (2017) The clinical practice guideline for the management of ARDS in Japan. J Intensive Care 5: 50. https://doi.org/10.1186/s40560-017-0222-3
65. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, Adhikari NKJ, Amato MBP, Branson R, Brower RG, Ferguson ND, Gajic O, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Pesenti A, Ranieri VM, Rubenfeld GD, Rubin E, Seckel M, Slutsky AS, Talmor D, Thompson BT, Wunsch H, Uleryk E, Brozek J, Brochard LJ, American Thoracic Society ESoICM, Society of Critical Care M, (2017) An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 195: 1253-1263. https://doi.org/10.1164/rccm.201703-0548ST
66. Alsaghir AH, Martin CM, (2008) Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. Crit Care Med 36: 603-609. https://doi.org/10.1097/01.CCM.0000299739.98236.05
67. Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L, (2008) The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty

and recommendations for research. Intensive Care Med 34: 1002-1011. https://doi.org/10.1007/s00134-008-1062-3

68. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, Caspani L, Raimondi F, Bordone G, Iapichino G, Mancebo J, Guerin C, Ayzac L, Blanch L, Fumagalli R, Tognoni G, Gattinoni L, Prone-Supine IISG, (2009) Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 302: 1977-1984. https://doi.org/10.1001/jama.2009.1614
69. Sud S, Sud M, Friedrich JO, Adhikari NK, (2008) Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. CMAJ 178: 1153-1161. https://doi.org/10.1503/cmaj.071802
70. Mancebo J, Fernandez R, Blanch L, Rialp G, Gordo F, Ferrer M, Rodriguez F, Garro P, Ricart P, Vallverdu I, Gich I, Castano J, Saura P, Dominguez G, Bonet A, Albert RK, (2006) A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 173: 1233-1239. https://doi.org/10.1164/rccm.200503-353OC
71. Tiruvoipati R, Bangash M, Manktelow B, Peek GJ, (2008) Efficacy of prone ventilation in adult patients with acute respiratory failure: a meta-analysis. J Crit Care 23: 101-110. https://doi.org/10.1016/j.jcrc.2007.09.003
72. Bloomfield R, Noble DW, Sudlow A, (2015) Prone position for acute respiratory failure in adults. Cochrane Database Syst Rev: CD008095. https://doi.org/10.1002/14651858.CD008095.pub2
73. Miyamoto K, Kawazoe Y, Yasuda M, Shibata N, Nakashima T, Kida M, Kato S, (2014) Oxygenation improves during the first 8 h of extended-duration prone positioning in patients with respiratory failure: a retrospective study. J Intensive Care 2: 52. https://doi.org/10.1186/s40560-014-0052-5
74. Voggenreiter G, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, Bock E, Gotzen L, Obertacke U, Nast-Kolb D, (2005) Prone positioning improves oxygenation in post-traumatic lung injury--a prospective randomized trial. J Trauma 59: 333-341; discussion 341-333. https://doi.org/10.1097/01.ta.0000179952.95921.49
75. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, Arabi YM, Baroncelli F, Beitler JR, Bellani G, Bellingan G, Blackwood B, Bos LDJ, Brochard L, Brodie D, Burns KEA, Combes A, D'Arrigo S, De Backer D, Demoule A, Einav S, Fan E, Ferguson ND, Frat JP, Gattinoni L, Guerin C, Herridge MS, Hodgson C, Hough CL, Jaber S, Juffermans NP, Karagiannidis C, Kesecioglu J, Kwizera A, Laffey JG, Mancebo J, Matthay MA, McAuley DF, Mercat A, Meyer NJ, Moss M, Munshi L, Myatra SN, Ng Gong M, Papazian L, Patel BK, Pellegrini M, Perner A, Pesenti A, Piquilloud L, Qiu H, Ranieri MV, Riviello E, Slutsky AS, Stapleton RD, Summers C, Thompson TB, Valente Barbas CS, Villar J, Ware LB, Weiss B, Zampieri FG, Azoulay E, Cecconi M, European Society of Intensive Care Medicine Taskforce on A, (2023) ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 49: 727-759. https://doi.org/10.1007/s00134-023-07050-7
76. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, Calfee CS, Combes A, Daniel BM, Ferguson ND, Gong MN, Gotts JE, Herridge MS, Laffey JG, Liu KD, Machado FR, Martin TR, McAuley DF, Mercat A, Moss M, Mularski RA, Pesenti A, Qiu H, Ramakrishnan N, Ranieri VM, Riviello ED, Rubin E, Slutsky AS, Thompson BT, Twagirumugabe T, Ware LB, Wick KD, (2024) A New Global Definition of Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 209: 37-47. https://doi.org/10.1164/rccm.202303-0558WS
77. Gainnier M, Michelet P, Thirion X, Arnal JM, Sainty JM, Papazian L, (2003) Prone position and positive end-expiratory pressure in acute respiratory distress syndrome. Crit Care Med 31: 2719-2726. https://doi.org/10.1097/01.CCM.0000094216.49129.4B
78. Adamzik M, Bauer A, Bein T, Benk C, Bock E, Boeken U, Brückner U, Buchwald D, Chaberny I, Deja M, Delis S, Dembinski R, Dubb R, Ellger B, Fantl R, Fichtner F, Frohnhofen H, Gama de Abreu M, Haberthür C, Hennersdorf M, Hoeper M, Hofmann C, Janssens U, Kaisers U,

Karagiannidis C, Klotz S, Kluge S, Laudi S, Markstaller K, Mattner F, Mayer K, Mörer O, Muellenbach R, Müller A, Müller T, Müllges W, Neumann P, Neumann J, Ney L, Nicolai T, Pfeifer M, Putensen C, Quintel M, Ragaller M, Rossaint R, Rosseau S, Schädler D, Schaible T, Schönhofer B, Schreiter D, Seeber C, Tholen R, Stanić D, Ullrich R, Veit W, Veit M, Weber-Carstens S, Weiler N, Weiß B, Werdan K, Wrigge H. (2017) S3-Leitlinie Invasive Beatmung und Einsatz extrakorporaler Verfahren bei akuter respiratorischer Insuffizienz. *https://register.awmf.org/assets/guidelines/001-021l_S3_Invasive_Beatmung_2017-12.pdf*, accessed on 13.05.2024

79. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X, (2013) Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 188: 1428-1433. *https://doi.org/10.1164/rccm.201303-0593OC*
80. Ruste M, Bitker L, Yonis H, Riad Z, Louf-Durier A, Lissonde F, Perinel-Ragey S, Guerin C, Richard JC, (2018) Hemodynamic effects of extended prone position sessions in ARDS. Ann Intensive Care 8: 120. *https://doi.org/10.1186/s13613-018-0464-9*
81. Hering R, Vorwerk R, Wrigge H, Zinserling J, Schroder S, von Spiegel T, Hoeft A, Putensen C, (2002) Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. Intensive Care Med 28: 53-58. *https://doi.org/10.1007/s00134-001-1166-5*
82. Hering R, Wrigge H, Vorwerk R, Brensing KA, Schroder S, Zinserling J, Hoeft A, Spiegel TV, Putensen C, (2001) The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. Anesth Analg 92: 1226-1231. *https://doi.org/10.1097/00000539-200105000-00027*
83. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F, (2007) Prone positioning unloads the right ventricle in severe ARDS. Chest 132: 1440-1446. *https://doi.org/10.1378/chest.07-1013*
84. Matejovic M, Rokyta R, Jr., Radermacher P, Krouzecky A, Sramek V, Novak I, (2002) Effect of prone position on hepato-splanchnic hemodynamics in acute lung injury. Intensive Care Med 28: 1750-1755. *https://doi.org/10.1007/s00134-002-1524-y*
85. Gaudry S, Tuffet S, Lukaszewicz AC, Laplace C, Zucman N, Pocard M, Costaglioli B, Msika S, Duranteau J, Payen D, Dreyfuss D, Hajage D, Ricard JD, (2017) Prone positioning in acute respiratory distress syndrome after abdominal surgery: a multicenter retrospective study : SAPRONADONF (Study of Ards and PRONe position After abDOmiNal surgery in France). Ann Intensive Care 7: 21. *https://doi.org/10.1186/s13613-017-0235-z*
86. Weig T, Janitza S, Zoller M, Dolch ME, Miller J, Frey L, Kneidinger N, Johnson T, Schubert MI, Irlbeck M, (2014) Influence of abdominal obesity on multiorgan dysfunction and mortality in acute respiratory distress syndrome patients treated with prone positioning. J Crit Care 29: 557-561. *https://doi.org/10.1016/j.jcrc.2014.02.010*
87. Danziger J, Chen KP, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ, (2016) Obesity, Acute Kidney Injury, and Mortality in Critical Illness. Crit Care Med 44: 328-334. *https://doi.org/10.1097/CCM.0000000000001398*
88. De Jong A, Molinari N, Sebbane M, Prades A, Futier E, Jung B, Chanques G, Jaber S, (2013) Feasibility and effectiveness of prone position in morbidly obese patients with ARDS: a case-control clinical study. Chest 143: 1554-1561. *https://doi.org/10.1378/chest.12-2115*
89. Beuret P, Carton MJ, Nourdine K, Kaaki M, Tramoni G, Ducreux JC, (2002) Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study. Intensive Care Med 28: 564-569. *https://doi.org/10.1007/s00134-002-1266-x*
90. Roth C, Ferbert A, Deinsberger W, Kleffmann J, Kastner S, Godau J, Schuler M, Tryba M, Gehling M, (2014) Does prone positioning increase intracranial pressure? A retrospective analysis of

patients with acute brain injury and acute respiratory failure. Neurocrit Care 21: 186-191. https://doi.org/10.1007/s12028-014-0004-x

91. Reinprecht A, Greher M, Wolfsberger S, Dietrich W, Illievich UM, Gruber A, (2003) Prone position in subarachnoid hemorrhage patients with acute respiratory distress syndrome: effects on cerebral tissue oxygenation and intracranial pressure. Crit Care Med 31: 1831-1838. https://doi.org/10.1097/01.CCM.0000063453.93855.0A
92. Nekludov M, Bellander BM, Mure M, (2006) Oxygenation and cerebral perfusion pressure improved in the prone position. Acta Anaesthesiol Scand 50: 932-936. https://doi.org/10.1111/j.1399-6576.2006.01099.x
93. Thelandersson A, Cider A, Nellgard B, (2006) Prone position in mechanically ventilated patients with reduced intracranial compliance. Acta Anaesthesiol Scand 50: 937-941. https://doi.org/10.1111/j.1399-6576.2006.01037.x
94. Wright JM, Gerges C, Shammassian B, Labak CM, Herring EZ, Miller B, Alkhachroum A, Kottapally M, Huang Wright C, Rodgers RB, Sedney C, Ngwenya LB, Stippler M, Sieg E, Babu MA, Hoffer A, Hejal R, (2021) Prone Position Ventilation in Neurologically Ill Patients: A Systematic Review and Proposed Protocol. Crit Care Med 49: e269-e278. https://doi.org/10.1097/CCM.0000000000004820
95. Bein T, Sabel K, Scherer A, Papp-Jambor C, Hekler M, Dubb R, Schlitt HJ, Taeger K, (2004) [Comparison of incomplete (135 degrees) and complete prone position (180 degrees) in patients with acute respiratory distress syndrome. Results of a prospective, randomised trial]. Anaesthesist 53: 1054-1060. https://doi.org/10.1007/s00101-004-0754-5
96. Girard R, Baboi L, Ayzac L, Richard JC, Guerin C, Proseva trial g, (2014) The impact of patient positioning on pressure ulcers in patients with severe ARDS: results from a multicentre randomised controlled trial on prone positioning. Intensive Care Med 40: 397-403. https://doi.org/10.1007/s00134-013-3188-1
97. Patton D, Latimer S, Avsar P, Walker RM, Moore Z, Gillespie BM, O'Connor T, Nugent L, Budri A, Brien NO, Chaboyer W, (2021) The effect of prone positioning on pressure injury incidence in adult intensive care unit patients: A meta-review of systematic reviews. Aust Crit Care https://doi.org/10.1016/j.aucc.2021.10.003
98. Gonzalez-Seguel F, Pinto-Concha JJ, Aranis N, Leppe J, (2021) Adverse Events of Prone Positioning in Mechanically Ventilated Adults With ARDS. Respir Care 66: 1898-1911. https://doi.org/10.4187/respcare.09194
99. Elmer N, Reisshauer A, Brehm K, Vockeroth C, Liebl ME, (2022) Long-term complications of prone position ventilation with relevance for acute and postacute rehabilitation: a systematic review of the literature. Eur J Phys Rehabil Med https://doi.org/10.23736/S1973-9087.22.07529-3
100. Elmer N, Liebl ME, Brehm K, Schwedtke C, Drebinger D, Pille C, Reißhauer A, (2022) Folgeschäden durch Beatmung in Bauchlage bei COVID-19 und ihre Relevanz für die Frührehabilitation – eine retrospektive Kohortenstudie. Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin https://doi.org/10.1055/a-1888-0020
101. Binda F, Galazzi A, Marelli F, Gambazza S, Villa L, Vinci E, Adamini I, Laquintana D, (2021) Complications of prone positioning in patients with COVID-19: A cross-sectional study. Intensive Crit Care Nurs 67: 103088. https://doi.org/10.1016/j.iccn.2021.103088
102. Li J, Luo J, Pavlov I, Perez Y, Tan W, Roca O, Tavernier E, Kharat A, McNicholas B, Ibarra-Estrada M, Vines DL, Bosch NA, Rampon G, Simpson SQ, Walkey AJ, Fralick M, Verma A, Razak F, Harris T, Laffey JG, Guerin C, Ehrmann S, Awake Prone Positioning Meta-Analysis G, (2022) Awake prone positioning for non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure: a systematic review and meta-analysis. Lancet Respir Med 10: 573-583. https://doi.org/10.1016/S2213-2600(22)00043-1

103. Schmid B, Griesel M, Fischer AL, Romero CS, Metzendorf MI, Weibel S, Fichtner F, (2022) Awake Prone Positioning, High-Flow Nasal Oxygen and Non-Invasive Ventilation as Non-Invasive Respiratory Strategies in COVID-19 Acute Respiratory Failure: A Systematic Review and Meta-Analysis. J Clin Med 11*https://doi.org/10.3390/jcm11020391*
104. Beran A, Mhanna M, Srour O, Ayesh H, Sajdeya O, Ghazaleh S, Mhanna A, Ghazaleh D, Khokher W, Maqsood A, Assaly R, (2022) Effect of Prone Positioning on Clinical Outcomes of Non-Intubated Subjects With COVID-19. Respir Care 67: 471-479. *https://doi.org/10.4187/respcare.09362*
105. Fazzini B, Page A, Pearse R, Puthucheary Z, (2022) Prone positioning for non-intubated spontaneously breathing patients with acute hypoxaemic respiratory failure: a systematic review and meta-analysis. Br J Anaesth 128: 352-362. *https://doi.org/10.1016/j.bja.2021.09.031*
106. Ehrmann S, Li J, Ibarra-Estrada M, Perez Y, Pavlov I, McNicholas B, Roca O, Mirza S, Vines D, Garcia-Salcido R, Aguirre-Avalos G, Trump MW, Nay MA, Dellamonica J, Nseir S, Mogri I, Cosgrave D, Jayaraman D, Masclans JR, Laffey JG, Tavernier E, Awake Prone Positioning Meta-Trial G, (2021) Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med 9: 1387-1395. *https://doi.org/10.1016/S2213-2600(21)00356-8*
107. Alhazzani W, Parhar KKS, Weatherald J, Al Duhailib Z, Alshahrani M, Al-Fares A, Buabbas S, Cherian SV, Munshi L, Fan E, Al-Hameed F, Chalabi J, Rahmatullah AA, Duan E, Tsang JLY, Lewis K, Lauzier F, Centofanti J, Rochwerg B, Culgin S, Nelson K, Abdukahil SA, Fiest KM, Stelfox HT, Tlayjeh H, Meade MO, Perri D, Solverson K, Niven DJ, Lim R, Moller MH, Belley-Cote E, Thabane L, Tamim H, Cook DJ, Arabi YM, Investigators C-PT, the Saudi Critical Care Trials G, (2022) Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial. JAMA 327: 2104-2113. *https://doi.org/10.1001/jama.2022.7993*
108. Fralick M, Colacci M, Munshi L, Venus K, Fidler L, Hussein H, Britto K, Fowler R, da Costa BR, Dhalla I, Dunbar-Yaffe R, Branfield Day L, MacMillan TE, Zipursky J, Carpenter T, Tang T, Cooke A, Hensel R, Bregger M, Gordon A, Worndl E, Go S, Mandelzweig K, Castellucci LA, Tamming D, Razak F, Verma AA, Investigators CPS, (2022) Prone positioning of patients with moderate hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ 376: e068585. *https://doi.org/10.1136/bmj-2021-068585*
109. Rosen J, von Oelreich E, Fors D, Jonsson Fagerlund M, Taxbro K, Skorup P, Eby L, Campoccia Jalde F, Johansson N, Bergstrom G, Frykholm P, Group PS, (2021) Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. Crit Care 25: 209. *https://doi.org/10.1186/s13054-021-03602-9*
110. Kluge S, Janssens U, Welte T, Weber-Carstens S, Schälte G, Spinner C, Malin J, Gastmeier P, Langer F, Bracht H, Westhoff M, Pfeifer M, Rabe K, Hoffmann F, Böttiger B, Weinmann-Menke J, Kersten A, P. B, Krawczyk M, Nehls W, Haase R, Müller O, Specker C, Nothacker M, Skoetz N, Marx G, Karagiannidis C. (2023) S3-Leitlinie - Empfehlungen zur Therapie von Patienten mit COVID-19. *https://register.awmf.org/assets/guidelines/113-001LGl_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19_2023-03.pdf*, accessed on 13.05.2024
111. Ibarra-Estrada M, Li J, Pavlov I, Perez Y, Roca O, Tavernier E, McNicholas B, Vines D, Marin-Rosales M, Vargas-Obieta A, Garcia-Salcido R, Aguirre-Diaz SA, Lopez-Pulgarin JA, Chavez-Pena Q, Mijangos-Mendez JC, Aguirre-Avalos G, Ehrmann S, Laffey JG, (2022) Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxemic respiratory failure: analysis of a randomized controlled trial. Crit Care 26: 84. *https://doi.org/10.1186/s13054-022-03950-0*
112. Ponnapa Reddy M, Subramaniam A, Afroz A, Billah B, Lim ZJ, Zubarev A, Blecher G, Tiruvoipati R, Ramanathan K, Wong SN, Brodie D, Fan E, Shekar K, (2021) Prone Positioning of

Nonintubated Patients With Coronavirus Disease 2019-A Systematic Review and Meta-Analysis. Crit Care Med 49: e1001-e1014. *https://doi.org/10.1097/CCM.0000000000005086*

113. Tan W, Xu DY, Xu MJ, Wang ZF, Dai B, Li LL, Zhao HW, Wang W, Kang J, (2021) The efficacy and tolerance of prone positioning in non-intubation patients with acute hypoxemic respiratory failure and ARDS: a meta-analysis. Ther Adv Respir Dis 15: 17534666211009407. *https://doi.org/10.1177/17534666211009407*
114. Esperatti M, Busico M, Fuentes NA, Gallardo A, Osatnik J, Vitali A, Wasinger EG, Olmos M, Quintana J, Saavedra SN, Lagazio AI, Andrada FJ, Kakisu H, Romano NE, Matarrese A, Mogadouro MA, Mast G, Moreno CN, Niquin GDR, Barbaresi V, Bruhn Cruz A, Ferreyro BL, Torres A, Argentine Collaborative Group on High F, Prone P, (2022) Impact of exposure time in awake prone positioning on clinical outcomes of patients with COVID-19-related acute respiratory failure treated with high-flow nasal oxygen: a multicenter cohort study. Crit Care 26: 16. *https://doi.org/10.1186/s13054-021-03881-2*
115. Papazian L, Schmidt M, Hajage D, Combes A, Petit M, Lebreton G, Rilinger J, Giani M, Le Breton C, Duburcq T, Jozwiak M, Wengenmayer T, Roux D, Parke R, Loundou A, Guervilly C, Boyer L, (2022) Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med 48: 270-280. *https://doi.org/10.1007/s00134-021-06604-x*
116. Poon WH, Ramanathan K, Ling RR, Yang IX, Tan CS, Schmidt M, Shekar K, (2021) Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care 25: 292. *https://doi.org/10.1186/s13054-021-03723-1*
117. Giani M, Rezoagli E, Guervilly C, Rilinger J, Duburcq T, Petit M, Textoris L, Garcia B, Wengenmayer T, Grasselli G, Pesenti A, Combes A, Foti G, Schmidt M, EuroPron EI, (2022) Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a pooled individual patient data analysis. Crit Care 26: 8. *https://doi.org/10.1186/s13054-021-03879-w*
118. Zaaqoq AM, Barnett AG, Griffee MJ, MacLaren G, Jacobs JP, Heinsar S, Suen JY, Bassi GL, Fraser JF, Dalton HJ, Peek GJ, Consortium C-CC, (2022) Beneficial Effect of Prone Positioning During Venovenous Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019. Crit Care Med 50: 275-285. *https://doi.org/10.1097/CCM.0000000000005296*
119. Liu C, Chen Y, Chen Y, Chen B, Xie G, Chen Y, (2021) Effects of prone positioning during extracorporeal membrane oxygenation for refractory respiratory failure: a systematic review. SN Compr Clin Med 3: 2109-2115. *https://doi.org/10.1007/s42399-021-01008-w*
120. Petit M, Fetita C, Gaudemer A, Treluyer L, Lebreton G, Franchineau G, Hekimian G, Chommeloux J, Pineton de Chambrun M, Brechot N, Luyt CE, Combes A, Schmidt M, (2022) Prone-Positioning for Severe Acute Respiratory Distress Syndrome Requiring Extracorporeal Membrane Oxygenation. Crit Care Med 50: 264-274. *https://doi.org/10.1097/CCM.0000000000005145*
121. Giani M, Martucci G, Madotto F, Belliato M, Fanelli V, Garofalo E, Forlini C, Lucchini A, Panarello G, Bottino N, Zanella A, Fossi F, Lissoni A, Peroni N, Brazzi L, Bellani G, Navalesi P, Arcadipane A, Pesenti A, Foti G, Grasselli G, (2021) Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome. A Multicenter Cohort Study and Propensity-matched Analysis. Ann Am Thorac Soc 18: 495-501. *https://doi.org/10.1513/AnnalsATS.202006-625OC*
122. Rilinger J, Zotzmann V, Bemtgen X, Schumacher C, Biever PM, Duerschmied D, Kaier K, Stachon P, von Zur Muhlen C, Zehender M, Bode C, Staudacher DL, Wengenmayer T, (2020) Prone positioning in severe ARDS requiring extracorporeal membrane oxygenation. Crit Care 24: 397. *https://doi.org/10.1186/s13054-020-03110-2*

123. Guerin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, Munshi L, Papazian L, Pesenti A, Vieillard-Baron A, Mancebo J, (2020) Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med 46: 2385-2396. *https://doi.org/10.1007/s00134-020-06306-w*
124. Chiumello D, Cressoni M, Racagni M, Landi L, Li Bassi G, Polli F, Carlesso E, Gattinoni L, (2006) Effects of thoraco-pelvic supports during prone position in patients with acute lung injury/acute respiratory distress syndrome: a physiological study. Crit Care 10: R87. *https://doi.org/10.1186/cc4933*
125. Kayambu G, Boots R, Paratz J, (2013) Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. Crit Care Med 41: 1543-1554. *https://doi.org/10.1097/CCM.0b013e31827ca637*
126. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, Schonhofer B, Stiller K, van de Leur H, Vincent JL, (2008) Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med 34: 1188-1199. *https://doi.org/10.1007/s00134-008-1026-7*
127. Li Z, Peng X, Zhu B, Zhang Y, Xi X, (2013) Active mobilization for mechanically ventilated patients: a systematic review. Arch Phys Med Rehabil 94: 551-561. *https://doi.org/10.1016/j.apmr.2012.10.023*
128. Adler J, Malone D, (2012) Early mobilization in the intensive care unit: a systematic review. Cardiopulm Phys Ther J 23: 5-13.
129. Fuest K, Schaller SJ, (2019) [Early mobilisation on the intensive care unit : What we know]. Med Klin Intensivmed Notfmed 114: 759-764. *https://doi.org/10.1007/s00063-019-0605-4*
130. Fuest K, Schaller SJ, (2018) Recent evidence on early mobilization in critical-Ill patients. Curr Opin Anaesthesiol 31: 144-150. *https://doi.org/10.1097/ACO.0000000000000568*
131. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, Larsson L, (2015) The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. Physiol Rev 95: 1025-1109. *https://doi.org/10.1152/physrev.00028.2014*
132. Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, Langhans C, Haas K, Radtke T, Kleber C, Spies C, Labeit S, Schuelke M, Spuler S, Spranger J, Weber-Carstens S, Fielitz J, (2014) Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med 40: 528-538. *https://doi.org/10.1007/s00134-014-3224-9*
133. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE, (2013) Acute skeletal muscle wasting in critical illness. JAMA 310: 1591-1600. *https://doi.org/10.1001/jama.2013.278481*
134. Fazzini B, Markl T, Costas C, Blobner M, Schaller SJ, Prowle J, Puthucheary Z, Wackerhage H, (2023) The rate and assessment of muscle wasting during critical illness: a systematic review and meta-analysis. Crit Care 27: 2. *https://doi.org/10.1186/s13054-022-04253-0*
135. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP, (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373: 1874-1882. *https://doi.org/10.1016/S0140-6736(09)60658-9*
136. Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, Heim M, Houle T, Kurth T, Latronico N, Lee J, Meyer MJ, Peponis T, Talmor D, Velmahos GC, Waak K, Walz JM, Zafonte R, Eikermann M, International Early S-gMRI, (2016) Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 388: 1377-1388. *https://doi.org/10.1016/S0140-6736(16)31637-3*

137. Ding N, Zhang Z, Zhang C, Yao L, Yang L, Jiang B, Wu Y, Jiang L, Tian J, (2019) What is the optimum time for initiation of early mobilization in mechanically ventilated patients? A network meta-analysis. PLoS One 14: e0223151. *https://doi.org/10.1371/journal.pone.0223151*
138. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneval J, Henderson A, Hugill K, Howard P, Roy A, Bonner S, Baudouin S, (2018) Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax 73: 213-221. *https://doi.org/10.1136/thoraxjnl-2016-209858*
139. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M, (2016) A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. Am J Respir Crit Care Med 193: 1101-1110. *https://doi.org/10.1164/rccm.201505-1039OC*
140. Clarissa C, Salisbury L, Rodgers S, Kean S, (2019) Early mobilisation in mechanically ventilated patients: a systematic integrative review of definitions and activities. J Intensive Care 7: 3. *https://doi.org/10.1186/s40560-018-0355-z*
141. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W, (2018) Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 46: e825-e873. *https://doi.org/10.1097/CCM.0000000000003299*
142. Monsees J, Moore Z, Patton D, Watson C, Nugent L, Avsar P, O'Connor T, (2022) A systematic review of the effect of early mobilization on length of stay for adults in the intensive care unit. Nurs Crit Care *https://doi.org/10.1111/nicc.12785*
143. Dong Z, Liu Y, Gai Y, Meng P, Lin H, Zhao Y, Xing J, (2021) Early rehabilitation relieves diaphragm dysfunction induced by prolonged mechanical ventilation: a randomised control study. BMC Pulm Med 21: 106. *https://doi.org/10.1186/s12890-021-01461-2*
144. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B, Chatterjee A, Young MP, (2016) Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA 315: 2694-2702. *https://doi.org/10.1001/jama.2016.7201*
145. Schujmann DS, Teixeira Gomes T, Lunardi AC, Zoccoler Lamano M, Fragoso A, Pimentel M, Peso CN, Araujo P, Fu C, (2020) Impact of a Progressive Mobility Program on the Functional Status, Respiratory, and Muscular Systems of ICU Patients: A Randomized and Controlled Trial. Crit Care Med 48: 491-497. *https://doi.org/10.1097/CCM.0000000000004181*
146. Zhou W, Yu L, Fan Y, Shi B, Wang X, Chen T, Yu H, Liu J, Wang X, Liu C, Zheng H, (2022) Effect of early mobilization combined with early nutrition on acquired weakness in critically ill patients (EMAS): A dual-center, randomized controlled trial. PLoS One 17: e0268599. *https://doi.org/10.1371/journal.pone.0268599*
147. Afxonidis G, Moysidis DV, Papazoglou AS, Tsagkaris C, Loudovikou A, Tagarakis G, Karapanagiotidis GT, Alexiou IA, Foroulis C, Anastasiadis K, (2021) Efficacy of Early and Enhanced Respiratory Physiotherapy and Mobilization after On-Pump Cardiac Surgery: A Prospective Randomized Controlled Trial. Healthcare (Basel) 9*https://doi.org/10.3390/healthcare9121735*

148. Cui Z, Li N, Gao C, Fan Y, Zhuang X, Liu J, Zhang J, Tan Q, (2020) Precision implementation of early ambulation in elderly patients undergoing off-pump coronary artery bypass graft surgery: a randomized-controlled clinical trial. BMC Geriatr 20: 404. *https://doi.org/10.1186/s12877-020-01823-1*
149. Ohbe H, Nakamura K, Uda K, Matsui H, Yasunaga H, (2021) Effect of Early Rehabilitation on Physical Function in Patients Undergoing Coronary Artery Bypass Grafting: A Nationwide Inpatient Database Study. J Clin Med 10*https://doi.org/10.3390/jcm10040618*
150. Hickmann CE, Castanares-Zapatero D, Deldicque L, Van den Bergh P, Caty G, Robert A, Roeseler J, Francaux M, Laterre PF, (2018) Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial. Crit Care Med 46: 1436-1443. *https://doi.org/10.1097/CCM.0000000000003263*
151. Chou W, Lai CC, Cheng KC, Yuan KS, Chen CM, Cheng AC, (2019) Effectiveness of early rehabilitation on patients with chronic obstructive lung disease and acute respiratory failure in intensive care units: A case-control study. Chron Respir Dis 16: 1479973118820310. *https://doi.org/10.1177/1479973118820310*
152. Coles SJ, Erdogan M, Higgins SD, Green RS, (2020) Impact of an early mobilization protocol on outcomes in trauma patients admitted to the intensive care unit: A retrospective pre-post study. J Trauma Acute Care Surg 88: 515-521. *https://doi.org/10.1097/TA.0000000000002588*
153. Elkbuli A, Fanfan D, Sutherland M, Newsome K, Morse J, Babcock J, McKenney M, (2022) The Association Between Early Versus Late Physical Therapy Initiation and Outcomes of Trauma Patients With and Without Traumatic Brain Injuries. J Surg Res 273: 34-43. *https://doi.org/10.1016/j.jss.2021.11.011*
154. Bakhru RN, McWilliams DJ, Wiebe DJ, Spuhler VJ, Schweickert WD, (2016) Intensive Care Unit Structure Variation and Implications for Early Mobilization Practices. An International Survey. Ann Am Thorac Soc 13: 1527-1537. *https://doi.org/10.1513/AnnalsATS.201601-078OC*
155. Dubb R, Nydahl P, Hermes C, Schwabbauer N, Toonstra A, Parker AM, Kaltwasser A, Needham DM, (2016) Barriers and Strategies for Early Mobilization of Patients in Intensive Care Units. Ann Am Thorac Soc 13: 724-730. *https://doi.org/10.1513/AnnalsATS.201509-586CME*
156. Nydahl P, Gunther U, Diers A, Hesse S, Kerschensteiner C, Klarmann S, Borzikowsky C, Kopke S, (2020) PROtocol-based MObilizaTION on intensive care units: stepped-wedge, cluster-randomized pilot study (Pro-Motion). Nurs Crit Care 25: 368-375. *https://doi.org/10.1111/nicc.12438*
157. Benjamin E, Roddy L, Giuliano KK, (2022) Management of patient tubes and lines during early mobility in the intensive care unit. Human Factors in Healthcare 2: 100017. *https://doi.org/https://doi.org/10.1016/j.hfh.2022.100017*
158. Klem HE, Tveiten TS, Beitland S, Malerod S, Kristoffersen DT, Dalsnes T, Nupen-Stieng MB, Larun L, (2021) Early activity in mechanically ventilated patients - a meta-analysis. Tidsskr Nor Laegeforen 141*https://doi.org/10.4045/tidsskr.20.0351*
159. Worraphan S, Thammata A, Chittawatanarat K, Saokaew S, Kengkla K, Prasannarong M, (2020) Effects of Inspiratory Muscle Training and Early Mobilization on Weaning of Mechanical Ventilation: A Systematic Review and Network Meta-analysis. Arch Phys Med Rehabil 101: 2002-2014. *https://doi.org/10.1016/j.apmr.2020.07.004*
160. (1976) Medical Research Council. Aids to the examination of the peripheral nervous system. In: Editor (ed)^(eds) Book Medical Research Council. Aids to the examination of the peripheral nervous system. City, pp.
161. Compston A, (2010) Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain : a journal of neurology 133: 2838-2844.

162. Wang J, Ren D, Liu Y, Wang Y, Zhang B, Xiao Q, (2020) Effects of early mobilization on the prognosis of critically ill patients: A systematic review and meta-analysis. Int J Nurs Stud 110: 103708. *https://doi.org/10.1016/j.ijnurstu.2020.103708*
163. Anekwe DE, Biswas S, Bussieres A, Spahija J, (2020) Early rehabilitation reduces the likelihood of developing intensive care unit-acquired weakness: a systematic review and meta-analysis. Physiotherapy 107: 1-10. *https://doi.org/10.1016/j.physio.2019.12.004*
164. Waldauf P, Jiroutkova K, Krajcova A, Puthucheary Z, Duska F, (2020) Effects of Rehabilitation Interventions on Clinical Outcomes in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Crit Care Med 48: 1055-1065. *https://doi.org/10.1097/CCM.0000000000004382*
165. Okada Y, Unoki T, Matsuishi Y, Egawa Y, Hayashida K, Inoue S, (2019) Early versus delayed mobilization for in-hospital mortality and health-related quality of life among critically ill patients: a systematic review and meta-analysis. J Intensive Care 7: 57. *https://doi.org/10.1186/s40560-019-0413-1*
166. Zhang L, Hu W, Cai Z, Liu J, Wu J, Deng Y, Yu K, Chen X, Zhu L, Ma J, Qin Y, (2019) Early mobilization of critically ill patients in the intensive care unit: A systematic review and meta-analysis. PLoS One 14: e0223185. *https://doi.org/10.1371/journal.pone.0223185*
167. Zang K, Chen B, Wang M, Chen D, Hui L, Guo S, Ji T, Shang F, (2020) The effect of early mobilization in critically ill patients: A meta-analysis. Nurs Crit Care 25: 360-367. *https://doi.org/10.1111/nicc.12455*
168. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL, (2017) The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 43: 171-183. *https://doi.org/10.1007/s00134-016-4612-0*
169. Wang YT, Lang JK, Haines KJ, Skinner EH, Haines TP, (2022) Physical Rehabilitation in the ICU: A Systematic Review and Meta-Analysis. Crit Care Med 50: 375-388. *https://doi.org/10.1097/CCM.0000000000005285*
170. Spies CD, Krampe H, Paul N, Denke C, Kiselev J, Piper SK, Kruppa J, Grunow JJ, Steinecke K, Gulmez T, Scholtz K, Rosseau S, Hartog C, Busse R, Caumanns J, Marschall U, Gersch M, Apfelbacher C, Weber-Carstens S, Weiss B, (2021) Instruments to measure outcomes of post-intensive care syndrome in outpatient care settings - Results of an expert consensus and feasibility field test. J Intensive Care Soc 22: 159-174. *https://doi.org/10.1177/1751143720923597*
171. Fuke R, Hifumi T, Kondo Y, Hatakeyama J, Takei T, Yamakawa K, Inoue S, Nishida O, (2018) Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. BMJ Open 8: e019998. *https://doi.org/10.1136/bmjopen-2017-019998*
172. Watanabe S, Liu K, Nakamura K, Kozu R, Horibe T, Ishii K, Yasumura D, Takahashi Y, Nanba T, Morita Y, Kanaya T, Suzuki S, Lefor AK, Katsukawa H, Kotani T, (2022) Association between Early Mobilization in the ICU and Psychiatric Symptoms after Surviving a Critical Illness: A Multi-Center Prospective Cohort Study. J Clin Med 11*https://doi.org/10.3390/jcm11092587*
173. Hodgson CL, Bailey M, Bellomo R, Berney S, Buhr H, Denehy L, Gabbe B, Harrold M, Higgins A, Iwashyna TJ, Papworth R, Parke R, Patman S, Presneill J, Saxena M, Skinner E, Tipping C, Young P, Webb S, Trial of Early A, Mobilization Study I, (2016) A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU. Crit Care Med 44: 1145-1152. *https://doi.org/10.1097/CCM.0000000000001643*
174. Amundadottir OR, Jónasdóttir RJ, Sigvaldason K, Gunnsteinsdottir E, Haraldsdottir B, Sveinsson T, Sigurdsson GH, Dean E, (2019) Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up. European Journal of Physiotherapy 23: 68-78. *https://doi.org/10.1080/21679169.2019.1645880*

175. Menges D, Seiler B, Tomonaga Y, Schwenkglenks M, Puhan MA, Yebyo HG, (2021) Systematic early versus late mobilization or standard early mobilization in mechanically ventilated adult ICU patients: systematic review and meta-analysis. Crit Care 25: 16. *https://doi.org/10.1186/s13054-020-03446-9*
176. Liang S, Chau JPC, Lo SHS, Zhao J, Choi KC, (2021) Effects of nonpharmacological delirium-prevention interventions on critically ill patients' clinical, psychological, and family outcomes: A systematic review and meta-analysis. Aust Crit Care 34: 378-387. *https://doi.org/10.1016/j.aucc.2020.10.004*
177. Ribeiro BC, Poca J, Rocha AMC, Cunha C, Cunha KDC, Falcao LFM, Torres DDC, Rocha LSO, Rocha RSB, (2021) Different physiotherapy protocols after coronary artery bypass graft surgery: A randomized controlled trial. Physiother Res Int 26: e1882. *https://doi.org/10.1002/pri.1882*
178. Dong Z, Yu B, Zhang Q, Pei H, Xing J, Fang W, Sun Y, Song Z, (2016) Early Rehabilitation Therapy Is Beneficial for Patients With Prolonged Mechanical Ventilation After Coronary Artery Bypass Surgery. Int Heart J 57: 241-246. *https://doi.org/10.1536/ihj.15-316*
179. Nakamura K, Ohbe H, Uda K, Fushimi K, Yasunaga H, (2021) Early rehabilitation after acute myocardial infarction: A nationwide inpatient database study. J Cardiol 78: 456-462. *https://doi.org/10.1016/j.jjcc.2021.06.004*
180. Schaller SJ, Scheffenbichler FT, Bose S, Mazwi N, Deng H, Krebs F, Seifert CL, Kasotakis G, Grabitz SD, Latronico N, Houle T, Blobner M, Eikermann M, (2019) Influence of the initial level of consciousness on early, goal-directed mobilization: a post hoc analysis. Intensive Care Med 45: 201-210. *https://doi.org/10.1007/s00134-019-05528-x*
181. Pang Y, Li H, Zhao L, Zhang C, (2019) An Established Early Rehabilitation Therapy Demonstrating Higher Efficacy and Safety for Care of Intensive Care Unit Patients. Med Sci Monit 25: 7052-7058. *https://doi.org/10.12659/MSM.916210*
182. Bahouth MN, Power MC, Zink EK, Kozeniewski K, Kumble S, Deluzio S, Urrutia VC, Stevens RD, (2018) Safety and Feasibility of a Neuroscience Critical Care Program to Mobilize Patients With Primary Intracerebral Hemorrhage. Arch Phys Med Rehabil 99: 1220-1225. *https://doi.org/10.1016/j.apmr.2018.01.034*
183. Klein KE, Bena JF, Mulkey M, Albert NM, (2018) Sustainability of a nurse-driven early progressive mobility protocol and patient clinical and psychological health outcomes in a neurological intensive care unit. Intensive Crit Care Nurs 45: 11-17. *https://doi.org/10.1016/j.iccn.2018.01.005*
184. Maffei P, Wiramus S, Bensoussan L, Bienvenu L, Haddad E, Morange S, Fathallah M, Hardwigsen J, Viton JM, Le Treut YP, Albanese J, Gregoire E, (2017) Intensive Early Rehabilitation in the Intensive Care Unit for Liver Transplant Recipients: A Randomized Controlled Trial. Arch Phys Med Rehabil 98: 1518-1525. *https://doi.org/10.1016/j.apmr.2017.01.028*
185. Higgins SD, Erdogan M, Coles SJ, Green RS, (2019) Early mobilization of trauma patients admitted to intensive care units: A systematic review and meta-analyses. Injury 50: 1809-1815. *https://doi.org/10.1016/j.injury.2019.09.007*
186. Kayambu G, Boots R, Paratz J, (2015) Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. Intensive Care Med 41: 865-874. *https://doi.org/10.1007/s00134-015-3763-8*
187. Yagi M, Morita K, Matsui H, Michihata N, Fushimi K, Koyama T, Fujitani J, Yasunaga H, (2021) Outcomes After Intensive Rehabilitation for Mechanically Ventilated Patients: A Nationwide Retrospective Cohort Study. Arch Phys Med Rehabil 102: 280-289. *https://doi.org/10.1016/j.apmr.2020.09.389*
188. Gatty A, Samuel SR, Alaparthi GK, Prabhu D, Upadya M, Krishnan S, Amaravadi SK, (2020) Effectiveness of structured early mobilization protocol on mobility status of patients in medical

intensive care unit. Physiother Theory Pract: 1-13. https://doi.org/10.1080/09593985.2020.1840683
189. Kim T, Huh S, Kim SY, Han J, Lee SE, Cho WH, Kim YS, Jeon DS, Yeo HJ, (2019) ICU rehabilitation is associated with reduced long-term mortality from sepsis in patients with low skeletal muscle mass: a case control study. Ann Transl Med 7: 430. https://doi.org/10.21037/atm.2019.08.117
190. Goldfarb M, Semsar-Kazerooni K, Morais JA, Dima D, (2021) Early Mobilization in Older Adults with Acute Cardiovascular Disease. Age Ageing 50: 1166-1172. https://doi.org/10.1093/ageing/afaa253
191. Goldfarb M, Afilalo J, Chan A, Herscovici R, Cercek B, (2018) Early mobility in frail and non-frail older adults admitted to the cardiovascular intensive care unit. J Crit Care 47: 9-14. https://doi.org/10.1016/j.jcrc.2018.05.013
192. Fuest KE, Lorenz M, Grunow JJ, Weiss B, Morgeli R, Finkenzeller S, Bogdanski R, Heim M, Kapfer B, Kriescher S, Lingg C, Martin J, Ulm B, Jungwirth B, Blobner M, Schaller SJ, (2021) The Functional Trajectory in Frail Compared With Non-frail Critically Ill Patients During the Hospital Stay. Front Med (Lausanne) 8: 748812. https://doi.org/10.3389/fmed.2021.748812
193. Thiolliere F, Allaouchiche B, Boyer H, Marie M, Friggeri A, Vacheron CH, group AS, (2022) Association between out-of-bed mobilization during the ICU stay of elderly patients and long-term autonomy: A cohort study. J Crit Care 68: 10-15. https://doi.org/10.1016/j.jcrc.2021.11.007
194. Iwai K, Hisano T, Komada R, Miyai T, Sakai K, Torimoto M, Tsujita Y, (2021) Effect of Early Rehabilitation in the Intensive Care Unit by a Dedicated Therapist Using a Rehabilitation Protocol: A Single-center Retrospective Study. Prog Rehabil Med 6: 20210030. https://doi.org/10.2490/prm.20210030
195. Liu K, Shibata J, Fukuchi K, Takahashi K, Sonoo T, Ogura T, Goto T, (2022) Optimal timing of introducing mobilization therapy for ICU patients with sepsis. J Intensive Care 10: 22. https://doi.org/10.1186/s40560-022-00613-8
196. Borges DL, Silva MG, Silva LN, Fortes JV, Costa ET, Assuncao RP, Lima CM, da Silva Nina VJ, Bernardo-Filho M, Caputo DS, (2016) Effects of Aerobic Exercise Applied Early After Coronary Artery Bypass Grafting on Pulmonary Function, Respiratory Muscle Strength, and Functional Capacity: A Randomized Controlled Trial. J Phys Act Health 13: 946-951. https://doi.org/10.1123/jpah.2015-0614
197. Cordeiro ALL, Reis JRD, Cruz HBD, Guimaraes AR, Gardenghi G, (2021) Impact of early ambulation on functionality in patients undergoing valve replacement surgery. J Clin Transl Res 7: 754-758. https://doi.org/10.18053/jctres.07.202106.005
198. Bartolo M, Bargellesi S, Castioni CA, Bonaiuti D, Intensive C, Neurorehabilitation Italian Study G, Antenucci R, Benedetti A, Capuzzo V, Gamna F, Radeschi G, Citerio G, Colombo C, Del Casale L, Recubini E, Toska S, Zanello M, D'Aurizio C, Spina T, Del Gaudio A, Di Rienzo F, Intiso D, Dallocchio G, Felisatti G, Lavezzi S, Zoppellari R, Gariboldi V, Lorini L, Melizza G, Molinero G, Mandala G, Pignataro A, Montis A, Napoleone A, Pilia F, Pisu M, Semerjian M, Pagliaro G, Nardin L, Scarponi F, Zampolini M, Zava R, Massetti MA, Piccolini C, Aloj F, Antonelli S, Zucchella C, (2016) Early rehabilitation for severe acquired brain injury in intensive care unit: multicenter observational study. Eur J Phys Rehabil Med 52: 90-100.
199. Bartolo M, Bargellesi S, Castioni CA, Intiso D, Fontana A, Copetti M, Scarponi F, Bonaiuti D, Intensive C, Neurorehabilitation Italian Study G, (2017) Mobilization in early rehabilitation in intensive care unit patients with severe acquired brain injury: An observational study. J Rehabil Med 49: 715-722. https://doi.org/10.2340/16501977-2269
200. Kim HJ, Lee Y, Sohng KY, (2014) Effects of bilateral passive range of motion exercise on the function of upper extremities and activities of daily living in patients with acute stroke. J Phys Ther Sci 26: 149-156. https://doi.org/10.1589/jpts.26.149

201. Booth K, Rivet J, Flici R, Harvey E, Hamill M, Hundley D, Holland K, Hubbard S, Trivedi A, Collier B, (2016) Progressive Mobility Protocol Reduces Venous Thromboembolism Rate in Trauma Intensive Care Patients: A Quality Improvement Project. J Trauma Nurs 23: 284-289. *https://doi.org/10.1097/JTN.0000000000000234*
202. Deng H, Chen J, Li F, Li-Tsang CW, Liu Q, Ma X, Ao M, Chen N, Zhou Y, Zhong X, Chen Z, Cao L, He G, Wu J, (2016) Effects of mobility training on severe burn patients in the BICU: A retrospective cohort study. Burns 42: 1404-1412. *https://doi.org/10.1016/j.burns.2016.07.029*
203. O'Neil AM, Rush C, Griffard L, Roggy D, Boyd A, Hartman B, (2022) 5 -Year Retrospective Analysis of a Vented Mobility Algorithm in the Burn ICU. J Burn Care Res *https://doi.org/10.1093/jbcr/irab248*
204. Mayer KP, Joseph-Isang E, Robinson LE, Parry SM, Morris PE, Neyra JA, (2020) Safety and Feasibility of Physical Rehabilitation and Active Mobilization in Patients Requiring Continuous Renal Replacement Therapy: A Systematic Review. Crit Care Med 48: e1112-e1120. *https://doi.org/10.1097/CCM.0000000000004526*
205. Toonstra AL, Zanni JM, Sperati CJ, Nelliot A, Mantheiy E, Skinner EH, Needham DM, (2016) Feasibility and Safety of Physical Therapy during Continuous Renal Replacement Therapy in the Intensive Care Unit. Ann Am Thorac Soc 13: 699-704. *https://doi.org/10.1513/AnnalsATS.201506-359OC*
206. Bento HA, Dummer D, Lohse BD, Noren C, Tonna JE, (2020) Walking While Dialyzing: A Retrospective Observation of Early Mobility and Ambulation for Patients on Continuous Renal Replacement Therapy. Crit Care Explor 2: e0131. *https://doi.org/10.1097/CCE.0000000000000131*
207. Ragland C, Ochoa L, Hartjes T, (2019) Early mobilisation in intensive care during renal replacement therapy: A quality improvement project. Intensive Crit Care Nurs 52: 22-27. *https://doi.org/10.1016/j.iccn.2018.12.005*
208. Wang YT, Haines TP, Ritchie P, Walker C, Ansell TA, Ryan DT, Lim PS, Vij S, Acs R, Fealy N, Skinner EH, (2014) Early mobilization on continuous renal replacement therapy is safe and may improve filter life. Crit Care 18: R161. *https://doi.org/10.1186/cc14001*
209. Perme C, Nalty T, Winkelman C, Kenji Nawa R, Masud F, (2013) Safety and Efficacy of Mobility Interventions in Patients with Femoral Catheters in the ICU: A Prospective Observational Study. Cardiopulm Phys Ther J 24: 12-17.
210. Titsworth WL, Hester J, Correia T, Reed R, Guin P, Archibald L, Layon AJ, Mocco J, (2012) The effect of increased mobility on morbidity in the neurointensive care unit. J Neurosurg 116: 1379-1388. *https://doi.org/10.3171/2012.2.JNS111881*
211. Avert Trial Collaboration Group, (2015) Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 386: 46-55. *https://doi.org/10.1016/S0140-6736(15)60690-0*
212. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, Lindley RI, Moodie M, Dewey H, Thrift AG, Donnan G, Group AC, (2016) Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). Neurology 86: 2138-2145. *https://doi.org/10.1212/WNL.0000000000002459*
213. Ringleb P, Köhrmann M, Jansen O, et al., (2022, in: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie.) Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie, DOI
214. Ma Z, Wang Q, Liu M, (2013) Early versus delayed mobilisation for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev: CD008346. *https://doi.org/10.1002/14651858.CD008346.pub2*

215. Young B, Moyer M, Pino W, Kung D, Zager E, Kumar MA, (2019) Safety and Feasibility of Early Mobilization in Patients with Subarachnoid Hemorrhage and External Ventricular Drain. Neurocrit Care 31: 88-96. https://doi.org/10.1007/s12028-019-00670-2
216. Yataco RA, Arnold SM, Brown SM, David Freeman W, Carmen Cononie C, Heckman MG, Partridge LW, Stucky CM, Mellon LN, Birst JL, Daron KL, Zapata-Cooper MH, Schudlich DM, (2019) Early Progressive Mobilization of Patients with External Ventricular Drains: Safety and Feasibility. Neurocrit Care 30: 414-420. https://doi.org/10.1007/s12028-018-0632-7
217. Shah SO, Kraft J, Ankam N, Bu P, Stout K, Melnyk S, Rincon F, Athar MK, (2018) Early Ambulation in Patients With External Ventricular Drains: Results of a Quality Improvement Project. J Intensive Care Med 33: 370-374. https://doi.org/10.1177/0885066616677507
218. Hester JM, Guin PR, Danek GD, Thomas JR, Titsworth WL, Reed RK, Vasilopoulos T, Fahy BG, (2017) The Economic and Clinical Impact of Sustained Use of a Progressive Mobility Program in a Neuro-ICU. Crit Care Med 45: 1037-1044. https://doi.org/10.1097/CCM.0000000000002305
219. Rand ML, Darbinian JA, (2015) Effect of an evidence-based mobility intervention on the level of function in acute intracerebral and subarachnoid hemorrhagic stroke patients on a neurointensive care unit. Arch Phys Med Rehabil 96: 1191-1199. https://doi.org/10.1016/j.apmr.2015.02.008
220. Karic T, Roe C, Nordenmark TH, Becker F, Sorteberg W, Sorteberg A, (2017) Effect of early mobilization and rehabilitation on complications in aneurysmal subarachnoid hemorrhage. J Neurosurg 126: 518-526. https://doi.org/10.3171/2015.12.JNS151744
221. Karic T, Roe C, Nordenmark TH, Becker F, Sorteberg A, (2016) Impact of early mobilization and rehabilitation on global functional outcome one year after aneurysmal subarachnoid hemorrhage. J Rehabil Med 48: 676-682. https://doi.org/10.2340/16501977-2121
222. Olkowski BF, Devine MA, Slotnick LE, Veznedaroglu E, Liebman KM, Arcaro ML, Binning MJ, (2013) Safety and feasibility of an early mobilization program for patients with aneurysmal subarachnoid hemorrhage. Phys Ther 93: 208-215. https://doi.org/10.2522/ptj.20110334
223. Braune S, Bojes P, Mecklenburg A, Angriman F, Soeffker G, Warnke K, Westermann D, Blankenberg S, Kubik M, Reichenspurner H, Kluge S, (2020) Feasibility, safety, and resource utilisation of active mobilisation of patients on extracorporeal life support: a prospective observational study. Ann Intensive Care 10: 161. https://doi.org/10.1186/s13613-020-00776-3
224. Lee H, Ko YJ, Suh GY, Yang JH, Park CM, Jeon K, Park YH, Chung CR, (2015) Safety profile and feasibility of early physical therapy and mobility for critically ill patients in the medical intensive care unit: Beginning experiences in Korea. J Crit Care 30: 673-677. https://doi.org/10.1016/j.jcrc.2015.04.012
225. Ko Y, Cho YH, Park YH, Lee H, Suh GY, Yang JH, Park CM, Jeon K, Chung CR, (2015) Feasibility and Safety of Early Physical Therapy and Active Mobilization for Patients on Extracorporeal Membrane Oxygenation. ASAIO J 61: 564-568. https://doi.org/10.1097/MAT.0000000000000239
226. Abrams D, Javidfar J, Farrand E, Mongero LB, Agerstrand CL, Ryan P, Zemmel D, Galuskin K, Morrone TM, Boerem P, Bacchetta M, Brodie D, (2014) Early mobilization of patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. Crit Care 18: R38. https://doi.org/10.1186/cc13746
227. Abrams D, Madahar P, Eckhardt CM, Short B, Yip NH, Parekh M, Serra A, Dubois RL, Saleem D, Agerstrand C, Scala P, Benvenuto L, Arcasoy SM, Sonett JR, Takeda K, Meier A, Beck J, Ryan P, Fan E, Hodgson CL, Bacchetta M, Brodie D, Investigators M-P, (2022) Early Mobilization during Extracorporeal Membrane Oxygenation for Cardiopulmonary Failure in Adults: Factors Associated with Intensity of Treatment. Ann Am Thorac Soc 19: 90-98. https://doi.org/10.1513/AnnalsATS.202102-151OC

228. Investigators E-PS, International EN, (2020) Early mobilisation during extracorporeal membrane oxygenation was safe and feasible: a pilot randomised controlled trial. Intensive Care Med 46: 1057-1059. https://doi.org/10.1007/s00134-020-05994-8
229. Hayes K, Holland AE, Pellegrino VA, Young M, Paul E, Hodgson CL, (2021) Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: A pilot randomised controlled trial. Aust Crit Care 34: 217-225. https://doi.org/10.1016/j.aucc.2020.07.008
230. Liu K, Ogura T, Takahashi K, Nakamura M, Ohtake H, Fujiduka K, Abe E, Oosaki H, Miyazaki D, Suzuki H, Nishikimi M, Lefor AK, Mato T, (2018) The safety of a novel early mobilization protocol conducted by ICU physicians: a prospective observational study. J Intensive Care 6: 10. https://doi.org/10.1186/s40560-018-0281-0
231. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, Annich GM, (2015) Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. Am J Respir Crit Care Med 191: 894-901. https://doi.org/10.1164/rccm.201409-1634OC
232. Scott JM, Downs M, Buxton R, Goetchius E, Crowell B, Ploutz-Snyder R, Hackney KJ, Ryder J, English K, Ploutz-Snyder LL, (2020) Disuse-Induced Muscle Loss and Rehabilitation: The National Aeronautics and Space Administration Bed Rest Study. Crit Care Explor 2: e0269. https://doi.org/10.1097/CCE.0000000000000269
233. Campbell M, Varley-Campbell J, Fulford J, Taylor B, Mileva KN, Bowtell JL, (2019) Effect of Immobilisation on Neuromuscular Function In Vivo in Humans: A Systematic Review. Sports Med 49: 931-950. https://doi.org/10.1007/s40279-019-01088-8
234. Dirks ML, Miotto PM, Goossens GH, Senden JM, Petrick HL, van Kranenburg J, van Loon LJC, Holloway GP, (2020) Short-term bed rest-induced insulin resistance cannot be explained by increased mitochondrial H2 O2 emission. J Physiol 598: 123-137. https://doi.org/10.1113/JP278920
235. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, Al Hasani H, Chadt A, Wenzel K, Koch S, Fielitz J, Kleber C, Faust K, Mai K, Spies CD, Luft FC, Boschmann M, Spranger J, Spuler S, (2013) Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. Am J Respir Crit Care Med 187: 387-396. https://doi.org/10.1164/rccm.201209-1649OC
236. Dos Santos C, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, Bain A, Guo Y, Advani A, Advani SL, Tomlinson G, Katzberg H, Streutker CJ, Cameron JI, Schols A, Gosker HR, Batt J, Group MI, Investigators RP, Canadian Critical Care Translational Biology G, (2016) Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay. A Pilot Study. Am J Respir Crit Care Med 194: 821-830. https://doi.org/10.1164/rccm.201512-2344OC
237. Stauble CG, Helming M, Martyn JA, Blobner M, Fink H, (2016) Neuromuscular Recovery Is Prolonged After Immobilization or Superimposition of Inflammation With Immobilization Compared to Inflammation Alone: Data From a Preclinical Model. Crit Care Med 44: e1097-e1110. https://doi.org/10.1097/CCM.0000000000001845
238. Nydahl P, Ruhl AP, Bartoszek G, Dubb R, Filipovic S, Flohr HJ, Kaltwasser A, Mende H, Rothaug O, Schuchhardt D, Schwabbauer N, Needham DM, (2014) Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. Crit Care Med 42: 1178-1186. https://doi.org/10.1097/CCM.0000000000000149
239. Fontela PC, Lisboa TC, Forgiarini-Junior LA, Friedman G, (2018) Early mobilization practices of mechanically ventilated patients: a 1-day point-prevalence study in southern Brazil. Clinics (Sao Paulo) 73: e241. https://doi.org/10.6061/clinics/2018/e241
240. Sibilla A, Nydahl P, Greco N, Mungo G, Ott N, Unger I, Rezek S, Gemperle S, Needham DM, Kudchadkar SR, (2020) Mobilization of Mechanically Ventilated Patients in Switzerland. J Intensive Care Med 35: 55-62. https://doi.org/10.1177/0885066617728486

241. Hermes C, Ochmann T, Deutsche Gesellschaft fur Internistische Intensivmedizin und Notfallmedizin e. V, Keienburg C, Deutsche Gesellschaft fur Fachkrankenpflege und Funktionsdienste e. V, Kegel M, Deutsche Gesellschaft Interdisziplinare Notfall- und Akutmedizin e. V, Schindele D, Deutsche Interdisziplinare Vereinigung fur Intensiv- und Notfallmedizin e. V, Klausmeier J, Deutsche Gesellschaft fur Kardiologie - Herz- und Kreislaufforschung e. V, Adrigan E, Osterreichische Gesellschaft fur Internistische und Allgemeine Intensivmedizin und Notfallmedizin e. V, (2022) [Intensive care of patients with [infarct-related] cardiogenic shock : Abridged version of the S1 guideline]. Med Klin Intensivmed Notfmed 117: 25-36. *https://doi.org/10.1007/s00063-022-00945-1*
242. Aquim EE, Bernardo WM, Buzzini RF, Azeredo NSG, Cunha LSD, Damasceno MCP, Deucher RAO, Duarte ACM, Librelato JT, Melo-Silva CA, Nemer SN, Silva S, Verona C, (2019) Brazilian Guidelines for Early Mobilization in Intensive Care Unit. Rev Bras Ter Intensiva 31: 434-443. *https://doi.org/10.5935/0103-507X.20190084*
243. Murray MJ, DeBlock H, Erstad B, Gray A, Jacobi J, Jordan C, McGee W, McManus C, Meade M, Nix S, Patterson A, Sands MK, Pino R, Tescher A, Arbour R, Rochwerg B, Murray CF, Mehta S, (2016) Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Crit Care Med 44: 2079-2103. *https://doi.org/10.1097/CCM.0000000000002027*
244. Wahab R, Yip NH, Chandra S, Nguyen M, Pavlovich KH, Benson T, Vilotijevic D, Rodier DM, Patel KR, Rychcik P, Perez-Mir E, Boyle SM, Berlin D, Needham DM, Brodie D, (2016) The implementation of an early rehabilitation program is associated with reduced length of stay: A multi-ICU study. J Intensive Care Soc 17: 2-11. *https://doi.org/10.1177/1751143715605118*
245. Conceicao T, Gonzales AI, Figueiredo F, Vieira DSR, Bundchen DC, (2017) Safety criteria to start early mobilization in intensive care units. Systematic review. Rev Bras Ter Intensiva 29: 509-519. *https://doi.org/10.5935/0103-507X.20170076*
246. Sakai T, Hoshino C, Okawa A, Wakabayashi K, Shigemitsu H, (2020) The Safety and Effect of Early Mobilization in the Intensive Care Unit According to Cancellation Criteria. Prog Rehabil Med 5: 20200016. *https://doi.org/10.2490/prm.20200016*
247. Yang R, Zheng Q, Zuo D, Zhang C, Gan X, (2021) Safety Assessment Criteria for Early Active Mobilization in Mechanically Ventilated ICU Subjects. Respir Care 66: 307-315. *https://doi.org/10.4187/respcare.07888*
248. Sommers J, Engelbert RH, Dettling-Ihnenfeldt D, Gosselink R, Spronk PE, Nollet F, van der Schaaf M, (2015) Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. Clin Rehabil 29: 1051-1063. *https://doi.org/10.1177/0269215514567156*
249. Fraser D, Spiva L, Forman W, Hallen C, (2015) Original Research: Implementation of an Early Mobility Program in an ICU. Am J Nurs 115: 49-58. *https://doi.org/10.1097/01.NAJ.0000475292.27985.fc*
250. McWilliams D, Weblin J, Atkins G, Bion J, Williams J, Elliott C, Whitehouse T, Snelson C, (2015) Enhancing rehabilitation of mechanically ventilated patients in the intensive care unit: a quality improvement project. J Crit Care 30: 13-18. *https://doi.org/10.1016/j.jcrc.2014.09.018*
251. Johns Hopkins Medicine/Armstrong Institute for Patient Safety and Quality. (2017) Early Mobility Guide for Reducing Ventilator-Associated Events in Mechanically Ventilated Patients. *https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/hais/tools/mvp/modules/technical/early-mobility-mvpguide.pdf*, accessed on 22.01.2023
252. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, Bradley S, Berney S, Caruana LR, Elliott D, Green M, Haines K, Higgins AM, Kaukonen KM, Leditschke IA, Nickels MR, Paratz J, Patman S, Skinner EH, Young PJ, Zanni JM, Denehy L, Webb SA, (2014) Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care 18: 658. *https://doi.org/10.1186/s13054-014-0658-y*

253. Presneill JJ, Bellomo R, Brickell K, Buhr H, Gabbe BJ, Gould DW, Harrold M, Higgins AM, Hurford S, Iwashyna T, Neto AS, Nichol A, Schaller SJ, Sivasuthan J, Tipping C, Webb S, Young P, Hodgson CL, (2021) Protocol and statistical analysis plan for the phase 3 randomised controlled Treatment of Invasively Ventilated Adults with Early Activity and Mobilisation (TEAM III) trial. Critical Care and Resuscitation 23: 262-272.
254. Boyd J, Paratz J, Tronstad O, Caruana L, McCormack P, Walsh J, (2018) When is it safe to exercise mechanically ventilated patients in the intensive care unit? An evaluation of consensus recommendations in a cardiothoracic setting. Heart Lung 47: 81-86. *https://doi.org/10.1016/j.hrtlng.2017.11.006*
255. Nydahl P, Ewers A, Brodda D, (2014) Complications related to early mobilization of mechanically ventilated patients on Intensive Care Units. Nurs Crit Care *https://doi.org/10.1111/nicc.12134*
256. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, Needham DM, (2017) Safety of Patient Mobilization and Rehabilitation in the Intensive Care Unit. Systematic Review with Meta-Analysis. Ann Am Thorac Soc 14: 766-777. *https://doi.org/10.1513/AnnalsATS.201611-843SR*
257. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L, Howard A, Dixon L, Leach S, Small R, Hite RD, Haponik E, (2008) Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 36: 2238-2243. *https://doi.org/10.1097/CCM.0b013e318180b90e*
258. Scheffenbichler FT, Teja B, Wongtangman K, Mazwi N, Waak K, Schaller SJ, Xu X, Barbieri S, Fagoni N, Cassavaugh J, Blobner M, Hodgson CL, Latronico N, Eikermann M, (2021) Effects of the Level and Duration of Mobilization Therapy in the Surgical ICU on the Loss of the Ability to Live Independently: An International Prospective Cohort Study. Crit Care Med 49: e247-e257. *https://doi.org/10.1097/CCM.0000000000004808*
259. Paton M, Lane R, Paul E, Cuthburtson GA, Hodgson CL, (2021) Mobilization During Critical Illness: A Higher Level of Mobilization Improves Health Status at 6 Months, a Secondary Analysis of a Prospective Cohort Study. Crit Care Med 49: e860-e869. *https://doi.org/10.1097/CCM.0000000000005058*
260. Watanabe S, Morita Y, Suzuki S, Kochi K, Ohno M, Liu K, Iida Y, (2021) Effects of the Intensity and Activity Time of Early Rehabilitation on Activities of Daily Living Dependence in Mechanically Ventilated Patients. Prog Rehabil Med 6: 20210054. *https://doi.org/10.2490/prm.20210054*
261. Kasotakis G, Schmidt U, Perry D, Grosse-Sundrup M, Benjamin J, Ryan C, Tully S, Hirschberg R, Waak K, Velmahos G, Bittner EA, Zafonte R, Cobb JP, Eikermann M, (2012) The surgical intensive care unit optimal mobility score predicts mortality and length of stay. Crit Care Med 40: 1122-1128. *https://doi.org/10.1097/CCM.0b013e3182376e6d*
262. Piva S, Dora G, Minelli C, Michelini M, Turla F, Mazza S, D'Ottavi P, Moreno-Duarte I, Sottini C, Eikermann M, Latronico N, (2015) The Surgical Optimal Mobility Score predicts mortality and length of stay in an Italian population of medical, surgical, and neurologic intensive care unit patients. J Crit Care 30: 1251-1257. *https://doi.org/10.1016/j.jcrc.2015.08.002*
263. Schaller SJ, Stauble CG, Suemasa M, Heim M, Duarte IM, Mensch O, Bogdanski R, Lewald H, Eikermann M, Blobner M, (2016) The German Validation Study of the Surgical Intensive Care Unit Optimal Mobility Score. J Crit Care 32: 201-206. *https://doi.org/10.1016/j.jcrc.2015.12.020*
264. Vollenweider R, Manettas AI, Hani N, de Bruin ED, Knols RH, (2022) Passive motion of the lower extremities in sedated and ventilated patients in the ICU - a systematic review of early effects and replicability of Interventions. PLoS One 17: e0267255. *https://doi.org/10.1371/journal.pone.0267255*

265. Rahiminezhad E, Sadeghi M, Ahmadinejad M, Mirzadi Gohari SI, Dehghan M, (2022) A randomized controlled clinical trial of the effects of range of motion exercises and massage on muscle strength in critically ill patients. BMC Sports Sci Med Rehabil 14: 96. https://doi.org/10.1186/s13102-022-00489-z
266. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, MacMillan RR, (1995) Effect of passive stretching on the wasting of muscle in the critically ill. Nutrition 11: 428-432.
267. Chiarici A, Andrenelli E, Serpilli O, Andreolini M, Tedesco S, Pomponio G, Gallo MM, Martini C, Papa R, Coccia M, Ceravolo MG, (2019) An Early Tailored Approach Is the Key to Effective Rehabilitation in the Intensive Care Unit. Arch Phys Med Rehabil 100: 1506-1514. https://doi.org/10.1016/j.apmr.2019.01.015
268. Sigler M, Nugent K, Alalawi R, Selvan K, Tseng J, Edriss H, Turner A, Valdez K, Krause D, (2016) Making of a Successful Early Mobilization Program for a Medical Intensive Care Unit. South Med J 109: 342-345. https://doi.org/10.14423/SMJ.0000000000000472
269. NICE. (2009) Rehabilitation after critical illness in adults. https://www.nice.org.uk/guidance/cg83, accessed on 19.01.2023
270. Meyer MJ, Stanislaus AB, Lee J, Waak K, Ryan C, Saxena R, Ball S, Schmidt U, Poon T, Piva S, Walz M, Talmor DS, Blobner M, Latronico N, Eikermann M, (2013) Surgical Intensive Care Unit Optimal Mobilisation Score (SOMS) trial: a protocol for an international, multicentre, randomised controlled trial focused on goal-directed early mobilisation of surgical ICU patients. BMJ Open 3: e003262. https://doi.org/10.1136/bmjopen-2013-003262
271. Nydahl P, Dubb R, Filipovic S, Hermes C, Juttner F, Kaltwasser A, Klarmann S, Mende H, Nessizius S, Rottensteiner C, (2017) [Algorithms for early mobilization in intensive care units]. Med Klin Intensivmed Notfmed 112: 156-162. https://doi.org/10.1007/s00063-016-0210-8
272. Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, Gabbe BJ, Gould DW, Harrold M, Higgins AM, Hurford S, Iwashyna TJ, Serpa Neto A, Nichol AD, Presneill JJ, Schaller SJ, Sivasuthan J, Tipping CJ, Webb S, Young PJ, (2022) Early Active Mobilization during Mechanical Ventilation in the ICU. N Engl J Med 387: 1747-1758. https://doi.org/10.1056/NEJMoa2209083
273. Moss M, (2022) Early Mobilization of Critical Care Patients - Still More to Learn. N Engl J Med 387: 1807-1808. https://doi.org/10.1056/NEJMe2212360
274. Bein T, Bischoff M, Bruckner U, Gebhardt K, Henzler D, Hermes C, Lewandowski K, Max M, Nothacker M, Staudinger T, Tryba M, Weber-Carstens S, Wrigge H, (2015) S2e guideline: positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders : Revision 2015: S2e guideline of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI). Anaesthesist 64 Suppl 1: 1-26. https://doi.org/10.1007/s00101-015-0071-1
275. Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, Young P, Zanni J, Buhr H, Higgins A, Presneill J, Berney S, (2014) Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart Lung 43: 19-24. https://doi.org/10.1016/j.hrtlng.2013.11.003
276. Tipping CJ, Bailey MJ, Bellomo R, Berney S, Buhr H, Denehy L, Harrold M, Holland A, Higgins AM, Iwashyna TJ, Needham D, Presneill J, Saxena M, Skinner EH, Webb S, Young P, Zanni J, Hodgson CL, (2016) The ICU Mobility Scale Has Construct and Predictive Validity and Is Responsive. A Multicenter Observational Study. Ann Am Thorac Soc 13: 887-893. https://doi.org/10.1513/AnnalsATS.201510-717OC
277. Yosef-Brauner O, Adi N, Ben Shahar T, Yehezkel E, Carmeli E, (2015) Effect of physical therapy on muscle strength, respiratory muscles and functional parameters in patients with intensive care unit-acquired weakness. Clin Respir J 9: 1-6. https://doi.org/10.1111/crj.12091
278. Winkelman C, Sattar A, Momotaz H, Johnson KD, Morris P, Rowbottom JR, Thornton JD, Feeney S, Levine A, (2018) Dose of Early Therapeutic Mobility: Does Frequency or Intensity Matter? Biol Res Nurs 20: 522-530. https://doi.org/10.1177/1099800418780492

279. Eggmann S, Verra ML, Luder G, Takala J, Jakob SM, (2018) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. PLoS One 13: e0207428. *https://doi.org/10.1371/journal.pone.0207428*
280. Investigators TS, the ACTG, Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, Buhr H, Gabbe BJ, Gould DW, Harrold M, Higgins AM, Hurford S, Iwashyna TJ, Serpa Neto A, Nichol AD, Presneill JJ, Schaller SJ, Sivasuthan J, Tipping CJ, Webb S, Young PJ, (2022) Early Active Mobilization during Mechanical Ventilation in the ICU. N Engl J Med 387: 1747-1758. *https://doi.org/10.1056/NEJMoa2209083*
281. Raurell-Torreda M, Arias-Rivera S, Marti JD, Frade-Mera MJ, Zaragoza-Garcia I, Gallart E, Velasco-Sanz TR, San Jose-Arribas A, Blazquez-Martinez E, group MO, (2021) Care and treatments related to intensive care unit-acquired muscle weakness: A cohort study. Aust Crit Care 34: 435-445. *https://doi.org/10.1016/j.aucc.2020.12.005*
282. Shimogai T, Izawa KP, Kawada M, Kuriyama A, (2019) Factors Affecting Discharge to Home of Medical Patients Treated in an Intensive Care Unit. Int J Environ Res Public Health 16*https://doi.org/10.3390/ijerph16224324*
283. Hsieh SJ, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, Garcia M, Prince D, Mills M, Fein D, Colman S, Gong MN, (2019) Staged Implementation of Awakening and Breathing, Coordination, Delirium Monitoring and Management, and Early Mobilization Bundle Improves Patient Outcomes and Reduces Hospital Costs. Crit Care Med 47: 885-893. *https://doi.org/10.1097/CCM.0000000000003765*
284. Matsuura Y, Ohno Y, Toyoshima M, Ueno T, (2022) Effects of non-pharmacologic prevention on delirium in critically ill patients: A network meta-analysis. Nurs Crit Care *https://doi.org/10.1111/nicc.12780*
285. Chen TJ, Traynor V, Wang AY, Shih CY, Tu MC, Chuang CH, Chiu HY, Chang HR, (2022) Comparative effectiveness of non-pharmacological interventions for preventing delirium in critically ill adults: A systematic review and network meta-analysis. Int J Nurs Stud 131: 104239. *https://doi.org/10.1016/j.ijnurstu.2022.104239*
286. SCCM. ICU Liberation Bundle (A-F). *https://www.sccm.org/Clinical-Resources/ICULiberation-Home/ABCDEF-Bundles*, accessed on 19.01.2023
287. Balas MC, Devlin JW, Verceles AC, Morris P, Ely EW, (2016) Adapting the ABCDEF Bundle to Meet the Needs of Patients Requiring Prolonged Mechanical Ventilation in the Long-Term Acute Care Hospital Setting: Historical Perspectives and Practical Implications. Semin Respir Crit Care Med 37: 119-135. *https://doi.org/10.1055/s-0035-1570361*
288. Collinsworth AW, Priest EL, Masica AL, (2020) Evaluating the Cost-Effectiveness of the ABCDE Bundle: Impact of Bundle Adherence on Inpatient and 1-Year Mortality and Costs of Care. Crit Care Med 48: 1752-1759. *https://doi.org/10.1097/CCM.0000000000004609*
289. Barnes-Daly MA, Phillips G, Ely EW, (2017) Improving Hospital Survival and Reducing Brain Dysfunction at Seven California Community Hospitals: Implementing PAD Guidelines Via the ABCDEF Bundle in 6,064 Patients. Crit Care Med 45: 171-178. *https://doi.org/10.1097/ccm.0000000000002149*
290. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, Byrum D, Carson SS, Devlin JW, Engel HJ, Esbrook CL, Hargett KD, Harmon L, Hielsberg C, Jackson JC, Kelly TL, Kumar V, Millner L, Morse A, Perme CS, Posa PJ, Puntillo KA, Schweickert WD, Stollings JL, Tan A, D'Agostino McGowan L, Ely EW, (2019) Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. Crit Care Med 47: 3-14. *https://doi.org/10.1097/CCM.0000000000003482*
291. (2022) Qualitätsindikatoren Intensivmedizin 4. Auflage 2022. *https://www.divi.de/joomlatools-files/docman-files/publikationen/peer-review/220310-qualitaetsindikatoren-intensivmedizin-divi-peer-review.pdf*, accessed on 26.08.2022

292. Frade-Mera MJ, Arias-Rivera S, Zaragoza-Garcia I, Marti JD, Gallart E, San Jose-Arribas A, Velasco-Sanz TR, Blazquez-Martinez E, Raurell-Torreda M, (2022) The impact of ABCDE bundle implementation on patient outcomes: A nationwide cohort study. Nurs Crit Care *https://doi.org/10.1111/nicc.12740*
293. Bounds M, Kram S, Speroni KG, Brice K, Luschinski MA, Harte S, Daniel MG, (2016) Effect of ABCDE Bundle Implementation on Prevalence of Delirium in Intensive Care Unit Patients. Am J Crit Care 25: 535-544. *https://doi.org/10.4037/ajcc2016209*
294. Balas MC, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, Peitz G, Gannon DE, Sisson J, Sullivan J, Stothert JC, Lazure J, Nuss SL, Jawa RS, Freihaut F, Ely EW, Burke WJ, (2014) Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 42: 1024-1036. *https://doi.org/10.1097/CCM.0000000000000129*
295. Chen CM, Cheng AC, Chou W, Selvam P, Cheng CM, (2021) Outcome of improved care bundle in acute respiratory failure patients. Nurs Crit Care 26: 380-385. *https://doi.org/10.1111/nicc.12530*
296. Martinez F, Donoso AM, Marquez C, Labarca E, (2017) Implementing a Multicomponent Intervention to Prevent Delirium Among Critically Ill Patients. Crit Care Nurse 37: 36-46. *https://doi.org/10.4037/ccn2017531*
297. Smith CD, Grami P, (2016) Feasibility and Effectiveness of a Delirium Prevention Bundle in Critically Ill Patients. Am J Crit Care 26: 19-27. *https://doi.org/10.4037/ajcc2017374*
298. Escalon MX, Lichtenstein AH, Posner E, Spielman L, Delgado A, Kolakowsky-Hayner SA, (2020) The Effects of Early Mobilization on Patients Requiring Extended Mechanical Ventilation Across Multiple ICUs. Crit Care Explor 2: e0119. *https://doi.org/10.1097/CCE.0000000000000119*
299. Appleton RT, Kinsella J, Quasim T, (2015) The incidence of intensive care unit-acquired weakness syndromes: A systematic review. J Intensive Care Soc 16: 126-136. *https://doi.org/10.1177/1751143714563016*
300. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphael JC, Outin H, Bastuji-Garin S, Groupe de Reflexion et d'Etude des Neuromyopathies en R, (2002) Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 288: 2859-2867. *https://doi.org/10.1001/jama.288.22.2859*
301. Morton RW, Murphy KT, McKellar SR, Schoenfeld BJ, Henselmans M, Helms E, Aragon AA, Devries MC, Banfield L, Krieger JW, Phillips SM, (2018) A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med 52: 376-384. *https://doi.org/10.1136/bjsports-2017-097608*
302. Ferrie S, Allman-Farinelli M, Daley M, Smith K, (2016) Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. JPEN J Parenter Enteral Nutr 40: 795-805. *https://doi.org/10.1177/0148607115618449*
303. Fetterplace K, Deane AM, Tierney A, Beach LJ, Knight LD, Presneill J, Rechnitzer T, Forsyth A, Gill BMT, Mourtzakis M, MacIsaac C, (2018) Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial). JPEN J Parenter Enteral Nutr 42: 1252-1262. *https://doi.org/10.1002/jpen.1166*
304. Lee ZY, Yap CSL, Hasan MS, Engkasan JP, Barakatun-Nisak MY, Day AG, Patel JJ, Heyland DK, (2021) The effect of higher versus lower protein delivery in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. Crit Care 25: 260. *https://doi.org/10.1186/s13054-021-03693-4*
305. Nydahl P, Schuchhardt D, Juttner F, Dubb R, Hermes C, Kaltwasser A, Mende H, Muller-Wolff T, Rothaug O, Schreiber T, (2020) Caloric consumption during early mobilisation of

mechanically ventilated patients in Intensive Care Units. Clin Nutr 39: 2442-2447. https://doi.org/10.1016/j.clnu.2019.10.028

306. Nakamura K, Nakano H, Naraba H, Mochizuki M, Takahashi Y, Sonoo T, Hashimoto H, Morimura N, (2021) High protein versus medium protein delivery under equal total energy delivery in critical care: A randomized controlled trial. Clin Nutr 40: 796-803. https://doi.org/10.1016/j.clnu.2020.07.036
307. de Azevedo JRA, Lima HCM, Frota P, Nogueira I, de Souza SC, Fernandes EAA, Cruz AM, (2021) High-protein intake and early exercise in adult intensive care patients: a prospective, randomized controlled trial to evaluate the impact on functional outcomes. BMC Anesthesiol 21: 283. https://doi.org/10.1186/s12871-021-01492-6
308. Kagan I, Cohen J, Bendavid I, Kramer S, Mesilati-Stahy R, Glass Y, Theilla M, Singer P, (2022) Effect of Combined Protein-Enriched Enteral Nutrition and Early Cycle Ergometry in Mechanically Ventilated Critically Ill Patients-A Pilot Study. Nutrients 14https://doi.org/10.3390/nu14081589
309. Heyland DK, Day A, Clarke GJ, Hough CT, Files DC, Mourtzakis M, Deutz N, Needham DM, Stapleton R, (2019) Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): a protocol of a multicentred, randomised controlled trial of combined cycle ergometry and amino acid supplementation commenced early during critical illness. BMJ Open 9: e027893. https://doi.org/10.1136/bmjopen-2018-027893
310. Kou K, Momosaki R, Miyazaki S, Wakabayashi H, Shamoto H, (2019) Impact of Nutrition Therapy and Rehabilitation on Acute and Critical Illness: A Systematic Review. J UOEH 41: 303-315. https://doi.org/10.7888/juoeh.41.303
311. Nakano H, Naraba H, Hashimoto H, Mochizuki M, Takahashi Y, Sonoo T, Ogawa Y, Matsuishi Y, Shimojo N, Inoue Y, Nakamura K, (2021) Novel protocol combining physical and nutrition therapies, Intensive Goal-directed REhabilitation with Electrical muscle stimulation and Nutrition (IGREEN) care bundle. Crit Care 25: 415. https://doi.org/10.1186/s13054-021-03827-8
312. Wappel S, Tran DH, Wells CL, Verceles AC, (2021) The Effect of High Protein and Mobility-Based Rehabilitation on Clinical Outcomes in Survivors of Critical Illness. Respir Care 66: 73-78. https://doi.org/10.4187/respcare.07840
313. Cameron JI, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, Friedrich JO, Mehta S, Lamontagne F, Levasseur M, Ferguson ND, Adhikari NK, Rudkowski JC, Meggison H, Skrobik Y, Flannery J, Bayley M, Batt J, dos Santos C, Abbey SE, Tan A, Lo V, Mathur S, Parotto M, Morris D, Flockhart L, Fan E, Lee CM, Wilcox ME, Ayas N, Choong K, Fowler R, Scales DC, Sinuff T, Cuthbertson BH, Rose L, Robles P, Burns S, Cypel M, Singer L, Chaparro C, Chow CW, Keshavjee S, Brochard L, Hebert P, Slutsky AS, Marshall JC, Cook D, Herridge MS, Investigators RP, Canadian Critical Care Trials G, (2016) One-Year Outcomes in Caregivers of Critically Ill Patients. N Engl J Med 374: 1831-1841. https://doi.org/10.1056/NEJMoa1511160
314. van Delft LMM, Valkenet K, Slooter AJC, Veenhof C, (2021) Family participation in physiotherapy-related tasks of critically ill patients: A mixed methods systematic review. J Crit Care 62: 49-57. https://doi.org/10.1016/j.jcrc.2020.11.014
315. Berry AB, Bennett J, Chaseling W, Cross Y, Cushway S, Hassan A, Jones S, Longhurst E, Moore R, Phillips DPE, (2017) Physical activity and movement: A guideline for critically ill adults
316. Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, Burns SM, Epstein SK, Esteban A, Fan E, Ferrer M, Fraser GL, Gong MN, Hough CL, Mehta S, Nanchal R, Patel S, Pawlik AJ, Schweickert WD, Sessler CN, Strom T, Wilson KC, Morris PE, Adults ACAHCoLfMVi, (2017) An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests. Am J Respir Crit Care Med 195: 120-133. https://doi.org/10.1164/rccm.201610-2075ST

317. Waldauf P, Hruskova N, Blahutova B, Gojda J, Urban T, Krajcova A, Fric M, Jiroutkova K, Rasova K, Duska F, (2021) Functional electrical stimulation-assisted cycle ergometry-based progressive mobility programme for mechanically ventilated patients: randomised controlled trial with 6 months follow-up. Thorax 76: 664-671. *https://doi.org/10.1136/thoraxjnl-2020-215755*
318. Fossat G, Baudin F, Courtes L, Bobet S, Dupont A, Bretagnol A, Benzekri-Lefevre D, Kamel T, Muller G, Bercault N, Barbier F, Runge I, Nay MA, Skarzynski M, Mathonnet A, Boulain T, (2018) Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. JAMA 320: 368-378. *https://doi.org/10.1001/jama.2018.9592*
319. Takaoka A, Utgikar R, Rochwerg B, Cook DJ, Kho ME, (2020) The Efficacy and Safety of In-Intensive Care Unit Leg-Cycle Ergometry in Critically Ill Adults. A Systematic Review and Meta-analysis. Ann Am Thorac Soc 17: 1289-1307. *https://doi.org/10.1513/AnnalsATS.202001-059OC*
320. Yu L, Jiang JX, Zhang Y, Chen YZ, Shi Y, (2020) Use of in-bed cycling combined with passive joint activity in acute respiratory failure patients receiving mechanical ventilation. Ann Palliat Med 9: 175-181. *https://doi.org/10.21037/apm.2020.02.12*
321. Machado ADS, Pires-Neto RC, Carvalho MTX, Soares JC, Cardoso DM, Albuquerque IM, (2017) Effects that passive cycling exercise have on muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients: a randomized clinical trial. J Bras Pneumol 43: 134-139. *https://doi.org/10.1590/S1806-37562016000000170*
322. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R, (2009) Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 37: 2499-2505. *https://doi.org/10.1097/CCM.0b013e3181a38937*
323. Bianchi T, Santos LJF, Lemos O, Sachetti A, Acqua AMD, Naue WS, Júnior LAF, Dias A, Vieira SRR, (2018) The Effect of Passive Cycle Ergometry Exercise on Dia-Phragmatic Motion of Invasive Mechanically Ventilated Critically Ill Patients in Intensive Care Unit: A Randomized Clinical Trial. International Journal of Physical Medicine and Rehabilitation 06: 1-8.
324. Parry SM, Berney S, Warrillow S, El-Ansary D, Bryant AL, Hart N, Puthucheary Z, Koopman R, Denehy L, (2014) Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. J Crit Care 29: 695 e691-697. *https://doi.org/10.1016/j.jcrc.2014.03.017*
325. Franca EET, Gomes JPV, De Lira JMB, Amaral TCN, Vilaca AF, Paiva Junior MDS, Elihimas Junior UF, Correia Junior MAV, Forgiarini Junior LA, Costa MJC, Andrade MA, Ribeiro LC, De Castro C, (2020) Acute effect of passive cycle-ergometry and functional electrical stimulation on nitrosative stress and inflammatory cytokines in mechanically ventilated critically ill patients: a randomized controlled trial. Braz J Med Biol Res 53: e8770. *https://doi.org/10.1590/1414-431X20208770*
326. Nickels MR, Aitken LM, Barnett AG, Walsham J, King S, Gale NE, Bowen AC, Peel BM, Donaldson SL, Mealing STJ, McPhail SM, (2020) Effect of in-bed cycling on acute muscle wasting in critically ill adults: A randomised clinical trial. J Crit Care 59: 86-93. *https://doi.org/10.1016/j.jcrc.2020.05.008*
327. Berney S, Hopkins RO, Rose JW, Koopman R, Puthucheary Z, Pastva A, Gordon I, Colantuoni E, Parry SM, Needham DM, Denehy L, (2021) Functional electrical stimulation in-bed cycle ergometry in mechanically ventilated patients: a multicentre randomised controlled trial. Thorax 76: 656-663. *https://doi.org/10.1136/thoraxjnl-2020-215093*
328. Medrinal C, Combret Y, Prieur G, Robledo Quesada A, Bonnevie T, Gravier FE, Dupuis Lozeron E, Frenoy E, Contal O, Lamia B, (2018) Comparison of exercise intensity during four early rehabilitation techniques in sedated and ventilated patients in ICU: a randomised cross-over trial. Crit Care 22: 110. *https://doi.org/10.1186/s13054-018-2030-0*

329. Kwakman RCH, Sommers J, Horn J, Nollet F, Engelbert RHH, van der Schaaf M, (2020) Steps to recovery: body weight-supported treadmill training for critically ill patients: a randomized controlled trial. Trials 21: 409. *https://doi.org/10.1186/s13063-020-04333-y*
330. Gama Lordello GG, Goncalves Gama GG, Lago Rosier G, Viana P, Correia LC, Fonteles Ritt LE, (2020) Effects of cycle ergometer use in early mobilization following cardiac surgery: a randomized controlled trial. Clin Rehabil 34: 450-459. *https://doi.org/10.1177/0269215520901763*
331. Windmoller P, Bodnar ET, Casagrande J, Dallazen F, Schneider J, Berwanger SA, Borghi-Silva A, Winkelmann ER, (2020) Physical Exercise Combined With CPAP in Subjects Who Underwent Surgical Myocardial Revascularization: A Randomized Clinical Trial. Respir Care 65: 150-157. *https://doi.org/10.4187/respcare.06919*
332. da Rosa Pinheiro DR, Cabeleira MEP, da Campo LA, Correa PS, Blauth A, Cechetti F, (2021) Effects of aerobic cycling training on mobility and functionality of acute stroke subjects: A randomized clinical trial. NeuroRehabilitation 48: 39-47. *https://doi.org/10.3233/NRE-201585*
333. Deutscher Ethikrat. (2020) Robotik für gute Pflege. *https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/deutsch/stellungnahme-robotik-fuer-gute-pflege.pdf*, accessed on 13.05.2024
334. Hermes C, Adrigan E, Dubb R, Kaltwasser A, Kuhn KF, Nessizius S, Nydahl P, Steinböck M, Schaller SJ, (2020) Reflektiert und mit Augenmaß einsetzen (Robotik zur Unterstützung der Frühmobilisierung). PflegeIntensiv: 14-21.
335. Krüger-Brand HE, (2020) Robotik in der Pflege: Ethikrat sieht großes Potenzial. Dtsche Arztebl 117(12): A-591 / B-508.
336. Frazzitta G, Zivi I, Valsecchi R, Bonini S, Maffia S, Molatore K, Sebastianelli L, Zarucchi A, Matteri D, Ercoli G, Maestri R, Saltuari L, (2016) Effectiveness of a Very Early Stepping Verticalization Protocol in Severe Acquired Brain Injured Patients: A Randomized Pilot Study in ICU. PLoS One 11: e0158030. *https://doi.org/10.1371/journal.pone.0158030*
337. Sommers J, Wieferink DC, Dongelmans DA, Nollet F, Engelbert RHH, van der Schaaf M, (2017) Body weight-supported bedside treadmill training facilitates ambulation in ICU patients: An interventional proof of concept study. J Crit Care 41: 150-155. *https://doi.org/10.1016/j.jcrc.2017.05.010*
338. Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, Chatzimichail A, Routsi C, Roussos C, Nanas S, (2009) Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. Crit Care 13: R161. *https://doi.org/10.1186/cc8123*
339. Gutierrez-Arias RE, Zapata-Quiroz CC, Prenafeta-Pedemonte BO, Nasar-Lillo NA, Gallardo-Zamorano DI, (2021) Effect of Neuromuscular Electrical Stimulation on the Duration of Mechanical Ventilation. Respir Care 66: 679-685. *https://doi.org/10.4187/respcare.08363*
340. Liu M, Luo J, Zhou J, Zhu X, (2020) Intervention effect of neuromuscular electrical stimulation on ICU acquired weakness: A meta-analysis. Int J Nurs Sci 7: 228-237. *https://doi.org/10.1016/j.ijnss.2020.03.002*
341. Zayed Y, Kheiri B, Barbarawi M, Chahine A, Rashdan L, Chintalapati S, Bachuwa G, Al-Sanouri I, (2020) Effects of neuromuscular electrical stimulation in critically ill patients: A systematic review and meta-analysis of randomised controlled trials. Aust Crit Care 33: 203-210. *https://doi.org/10.1016/j.aucc.2019.04.003*
342. Burke D, Gorman E, Stokes D, Lennon O, (2016) An evaluation of neuromuscular electrical stimulation in critical care using the ICF framework: a systematic review and meta-analysis. Clin Respir J 10: 407-420. *https://doi.org/10.1111/crj.12234*
343. Wageck B, Nunes GS, Silva FL, Damasceno MC, de Noronha M, (2014) Application and effects of neuromuscular electrical stimulation in critically ill patients: systematic review. Med Intensiva 38: 444-454. *https://doi.org/10.1016/j.medin.2013.12.003*

344. Jonkman AH, Frenzel T, McCaughey EJ, McLachlan AJ, Boswell-Ruys CL, Collins DW, Gandevia SC, Girbes ARJ, Hoiting O, Kox M, Oppersma E, Peters M, Pickkers P, Roesthuis LH, Schouten J, Shi ZH, Veltink PH, de Vries HJ, Shannon Weickert C, Wiedenbach C, Zhang Y, Tuinman PR, de Man AME, Butler JE, Heunks LMA, (2020) Breath-synchronized electrical stimulation of the expiratory muscles in mechanically ventilated patients: a randomized controlled feasibility study and pooled analysis. Crit Care 24: 628. *https://doi.org/10.1186/s13054-020-03352-0*
345. Rodriguez PO, Setten M, Maskin LP, Bonelli I, Vidomlansky SR, Attie S, Frosiani SL, Kozima S, Valentini R, (2012) Muscle weakness in septic patients requiring mechanical ventilation: protective effect of transcutaneous neuromuscular electrical stimulation. J Crit Care 27: 319 e311-318. *https://doi.org/10.1016/j.jcrc.2011.04.010*
346. Grunow JJ, Goll M, Carbon NM, Liebl ME, Weber-Carstens S, Wollersheim T, (2019) Differential contractile response of critically ill patients to neuromuscular electrical stimulation. Crit Care 23: 308. *https://doi.org/10.1186/s13054-019-2540-4*
347. Nakamura K, Kihata A, Naraba H, Kanda N, Takahashi Y, Sonoo T, Hashimoto H, Morimura N, (2019) Efficacy of belt electrode skeletal muscle electrical stimulation on reducing the rate of muscle volume loss in critically ill patients: A randomized controlled trial. J Rehabil Med 51: 705-711. *https://doi.org/10.2340/16501977-2594*
348. Segers J, Vanhorebeek I, Langer D, Charususin N, Wei W, Frickx B, Demeyere I, Clerckx B, Casaer M, Derese I, Derde S, Pauwels L, Van den Berghe G, Hermans G, Gosselink R, (2021) Early neuromuscular electrical stimulation reduces the loss of muscle mass in critically ill patients - A within subject randomized controlled trial. J Crit Care 62: 65-71. *https://doi.org/10.1016/j.jcrc.2020.11.018*
349. Fischer A, Spiegl M, Altmann K, Winkler A, Salamon A, Themessl-Huber M, Mouhieddine M, Strasser EM, Schiferer A, Paternostro-Sluga T, Hiesmayr M, (2016) Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: does neuromuscular electrical stimulation help? The Catastim 2 randomized controlled trial. Crit Care 20: 30. *https://doi.org/10.1186/s13054-016-1199-3*
350. Nakanishi N, Oto J, Tsutsumi R, Yamamoto T, Ueno Y, Nakataki E, Itagaki T, Sakaue H, Nishimura M, (2020) Effect of Electrical Muscle Stimulation on Upper and Lower Limb Muscles in Critically Ill Patients: A Two-Center Randomized Controlled Trial. Crit Care Med 48: e997-e1003. *https://doi.org/10.1097/CCM.0000000000004522*
351. Routsi C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki E, Markaki V, Zervakis D, Nanas S, (2010) Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. Crit Care 14: R74. *https://doi.org/10.1186/cc8987*
352. Fuest KE, Ulm B, Daum N, Lindholz M, Lorenz M, Blobner K, Langer N, Hodgson C, Herridge M, Blobner M, Schaller SJ, (2023) Clustering of critically ill patients using an individualized learning approach enables dose optimization of mobilization in the ICU. Crit Care 27: 1. *https://doi.org/10.1186/s13054-022-04291-8*
353. AWMF. (2012) AWMF Guidance Manual and Rules for Guideline Development. *https://www.awmf.org/fileadmin/user_upload/dateien/downloads_regelwerk/AWMF-Guidance_2013.pdf*, accessed on 12.05.2024
354. AWMF. Musterevidenztabelle. *https://www.awmf.org/fileadmin/user_upload/Leitlinien/AWMF-Regelwerk/Anhaenge/Anhang_06_Musterevidenztabelle.doc*, accessed on 01.09.2022
355. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. *https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence*, accessed on 13.05.2024
356. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH, (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64: 401-406. *https://doi.org/10.1016/j.jclinepi.2010.07.015*

357. AWMF. (2018) AWMF-Regel für das Leitlinienregister: Erklärung von Interessen und Umgang mit Interessenkonflikten bei Leitlinienvorhaben. *https://www.awmf.org/fileadmin/user_upload/dateien/downloads_regelwerk/02_20180117_AWMF-Regel_Interessenkonflikte_V2.4.pdf*, accessed on 13.05.2024